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Extrahepatic Manifestations of Hepatitis C Virus Infection

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Abstract

Chronic hepatitis C virus (HCV) infection causes progressive liver fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma. Additional to liver damage, HCV infection causes a variety of systemic disorders, some of which sometimes bear more severe morbidity than the liver disease itself. These extrahepatic manifestations represent a wide spectrum of disorders, ranging from the presence of a variety of clinically insignificant autoantibodies to diseases affecting a variety of organ systems. Mixed cryoglobulinemia is a common manifestation, and associated vasculitis can affect many organs (kidney, skin, and joints). The skin can also be affected by porphyria cutanea tarda and lichen planus. Other common extrahepatic manifestations include autoimmune disorders, lymphoproliferative disorders, and a number of neurological and neuropsychiatric disorders such as fatigue, depression, or cognitive impairment. Insulin resistance, diabetes mellitus, accelerated atherosclerosis, and increased cardiovascular disease morbidity and mortality have also been associated with chronic HCV infection. The existence and severity of extrahepatic manifestations do not correlate with the severity of liver disease, and the mainstay of treatment is HCV eradication. Patients with systemic manifestations of HCV infection should be prioritized for treatment, especially in the era of new interferon-free therapies with fewer side effects.

Keywords: chronic hepatitis C infection, extrahepatic manifestations, interferon therapy, direct-acting antiviral agents

1. Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus, a member of the *Flaviviridae* family. As a primarily hepatotropic virus, the main target of infection is hepatocytes, resulting in chronic inflammation in about 80% of cases of infection. It is well known that chronic hepatitis

C leads to cirrhosis, the terminal stage of liver disease, and hepatocellular carcinoma. It is, however, less known that chronic HCV infection leads to a series of systemic disorders and diseases that can often leave greater health consequences than the liver disease alone. These disorders are commonly called extrahepatic manifestations of chronic hepatitis C and encompass a wide spectrum of conditions, from a clinically insignificant presence of different auto-antibodies to vasculitis, skin disease, kidney damage, lymphoproliferative disorders, diabetes, various neurological and neuropsychiatric changes, and even increased cardiovascular morbidity and mortality [1]. Extrahepatic manifestations in any form may appear in up to 74% of patients with chronic HCV infection and may long precede manifest hepatic disease presenting with various nonspecific health impairments including malaise, fatigue, nausea, weight loss, and musculoskeletal pain [2]. Specific extrahepatic manifestations of chronic hepatitis C can be divided according to the affected organ or organ system, pathological mechanism, or the strength of available evidence connecting them to chronic hepatitis C infection. Some of the extrahepatic manifestations according to organ system and proposed pathological mechanism are shown in **Tables 1** and **2**. The fact that the severity of these disorders does not necessarily correlate with the severity of hepatic disease is of great clinical significance because even in cases of mildly active chronic hepatitis, a considerable disruption of overall health and quality

Hematopoietic	Essential mixed cryoglobulinemia Monoclonal gammopathy B-cell non-Hodgkin lymphoma
Skin	Leukocytoclastic vasculitis Porphyria cutanea tarda Lichen planus
Kidneys	Membranoproliferative glomerulonephritis Membranous nephropathy Renal impairment
Immunological	Autoimmune antibodies: rheumatoid factor, antinuclear, antithyroid, anticardiolipin, anti-smooth muscle antibodies
Thyroid	Thyroiditis Hypothyroidism Hyperthyroidism
Endocrine and exocrine glands	Type 2 diabetes mellitus Sicca syndrome
Musculoskeletal	Arthralgia/myalgia
Neurological and neuropsychiatric disorders	Fatigue Depression Impaired cognitive function Sensory or sensorimotor polyneuropathy Mononeuritis multiplex
Cardiovascular	Accelerated atherosclerosis Increased rate of cardiovascular and neurovascular incident and peripheral artery disease Increased mortality from cardiovascular and neurovascular incidents

Table 1. The most common extrahepatic manifestations of chronic hepatitis C according to organ system involvement.

Autoimmune mechanism	Proliferative effect	Inflammatory/metabolic	Other mechanism
Autoantibodies	Essential mixed cryoglobulinemia	Insulin resistance and diabetes mellitus	Porphyria cutanea tarda
Thyroiditis	Monoclonal gammopathy	Fatigue/malaise	
Hepatitis	Non-Hodgkin lymphoma	Depression	
Sicca syndrome		Cognitive function damage	
Arthralgia/myalgia		Cardiovascular disease (coronary disease, stroke)	

Table 2. Proposed pathogenetic mechanism through which chronic HCV infection leads to extrahepatic manifestations.

of life can occur. On the other hand, numerous studies have shown that treatment of chronic HCV infection accomplishes the resolution of extrahepatic disease or greatly increases function of the affected organ and lowers accompanying morbidity and mortality risks. Because of this reason, it is accepted and highlighted in current European guidelines, as well as Croatian recommendations for treatment of chronic hepatitis C infection, that patients with extrahepatic manifestations should be prioritized for treatment, regardless of the activity/severity of their liver disease alone [3, 4].

2. Essential mixed cryoglobulinemia

Essential mixed cryoglobulinemia or type II cryoglobulinemia is classified into the group of lymphoproliferative disorders in which clonal B lymphocyte expansion leads to immunoglobulin production—polyclonal immunoglobulin (Ig) G class and monoclonal IgM as rheumatoid factor (RF)—leading to development of immune complexes that precipitate in the cold and are therefore called cryoglobulins. As a consequence of the precipitation of cryoglobulin complexes in small- and middle-sized blood vessels, the occurring complement activation leads to endothelial damage and cryoglobulinemic vasculitis [5]. The syndrome can affect blood vessels in different organs and manifest on the skin, large joints, peripheral nerves, or kidneys. Cryoglobulins are present in about 50% of patients with chronic hepatitis C infection, but do not always cause clinically manifest cryoglobulinemic vasculitis. On the other hand, over 90% of patients with essential mixed cryoglobulinemia have chronic hepatitis C infection. The skin is commonly affected in cryoglobulinemic syndrome manifesting as palpable purpura as a consequence of leukocytoclastic vasculitis [6]. Joint involvement manifests with arthralgias; perineural vasculitis is a cause of distal sensory or sensorimotor polyneuropathy, while kidney involvement most often leads to membranoproliferative glomerulonephritis with renal function impairment. Diagnosis is based on cryoglobulin presence, elevated RF, and immunofluorescence of complement fixing IgM in affected tissues. It is important to note that many studies have shown clinical manifestations of essential mixed cryoglobulinemia to withdraw

after successful HCV infection treatment and that the presence of mixed cryoglobulinemia is associated with a reduced virological response rate [7]. Withdrawal of essential mixed cryoglobulinemia, with low recurrence levels, has been established earlier with interferon therapy, and recently some smaller scale studies showed a very good effect of combined direct-acting antiviral therapy (so-called “interferon-free” therapy) in cryoglobulin clearance, renal function improvement, and proteinuria reduction [8, 9]. The success rates seem to be lower than those observed in large registration studies, but the fact the treatment is new and that sample sizes were relatively small should be taken into account. It is important to highlight that, in some patients, interferon therapy can lead to the worsening of clinical manifestations and that in everyday practice optimal antiviral therapy with direct-acting antiviral drugs represents the standard of care for patients with clinically mild to moderate cryoglobulinemic vasculitis. In severe cases additional therapy modalities such as rituximab, corticosteroids, and plasmapheresis may be used before starting antiviral therapy. For refractory forms of cryoglobulinemia, cyclophosphamide and other immunosuppressants are sometimes used.

3. B-cell lymphoma and monoclonal gammopathies

Hepatitis C virus is primarily hepatotropic, but it has also been shown to be lymphotropic, and a connection between chronic HCV infection and B-cell non-Hodgkin lymphoma (NHL) has been established [10, 11]. It is assumed that chronic B lymphocyte stimulation by the HCV antigen leads to monoclonal B-cell expansion present in mixed cryoglobulinemia. This seems to predispose to NHL occurrence, with studies showing increased risk relative to the general population [12]. In a retrospective study comparing untreated HCV-infected patients to those treated with interferon, it has been shown that the rates of malignant lymphoma occurrence (diffuse large cell lymphoma and follicular lymphoma) were significantly higher in untreated patients, as well as in those who did not achieve sustained virologic response (SVR), compared to those who were cured [13]. The importance of chronic HCV infection in lymphoma development was additionally confirmed with reports of successful NHL remission after HCV eradication. Results with new interferon-free therapies are so far only available as case reports but point to lymphoma withdrawal after hepatitis C eradication. It can be expected that the wide use of new therapies will show results in larger cohorts of patients.

There are studies suggesting HCV to be a risk factor for monoclonal gammopathies, but the results are inconsistent, and a routine screening of patients with chronic hepatitis C for monoclonal gammopathies is not recommended. In patients with HCV infection, polyclonal or oligoclonal hypergammaglobulinemia (mostly IgG) is present. The gamma globulin level often correlates with disease severity on liver biopsy, and its decrease after successful HCV treatment has been noted.

4. Kidney impairment

Chronic hepatitis C infection is connected with glomerular disease which is most probably a consequence of immune complex deposition in glomerular capillaries. The most common

form of kidney disease is membranoproliferative glomerulonephritis, typically connected with essential mixed cryoglobulinemia, while membranous nephropathy is less common [14, 15]. Other non-cryoglobulin-based renal diseases described in HCV-infected patients include IgA nephropathy, postinfectious glomerulonephritis, as well as focal and segmental glomerulosclerosis. Patients most often present with proteinuria and microhematuria with different degrees of renal impairment and with renal biopsy showing glomerular immune complex deposition. Acute nephrotic or nephritic syndrome with new onset of arterial hypertension is also possible. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines thus recommend screening for renal impairment at the time of HCV infection diagnosis and then once a year by determining serum creatinine and performing urinalysis. All patients with chronic kidney disease should also be tested for HCV infection [16]. The existence of renal impairment, especially membranoproliferative glomerulonephritis, is an indication for HCV infection treatment. Until now the standard of treatment was combined interferon and ribavirin (with necessary precaution and kidney function-adjusted dosage), while rituximab, corticosteroids, or immunosuppressants are added in patients with severe cryoglobulinemic vasculitis. Data about the efficacy of new interferon-free therapies in this indication is only available from studies involving a relatively small number of patients, but it can be expected that it could significantly change the clinical presentation and improve treatment of this group of patients [8].

5. Skin manifestations

Porphyria cutanea tarda (PCT) is a disease caused by the reduced activity of the hepatic uroporphyrinogen decarboxylase (UROD) which leads to accumulation of uroporphyrinogen in the blood and urine and is the most common porphyria. PCT can be inherited (autosomal dominant) or acquired (sporadic), and exactly this form was connected with HCV infection in many studies. Meta-analysis that included 50 studies and a total of 2167 patients with PCT showed that the prevalence of HCV infection was around 50%, while the frequency of PCT in patients with chronic HCV infection is about 1–5% [17]. The exact mechanism by which HCV can cause or induce PTC is not known, but it is presumed to be mediated through changes in iron metabolism. Namely, increased iron saturation, estrogens, and alcohol consumption can provoke or induce PCT. Skin changes develop as a consequence of photosensitivity and skin friability and, upon sun exposure and/or minor trauma, manifest as erythema and bullae which may turn hemorrhagic [18, 19]. In later stages hyperpigmentation, hypopigmentation, hirsutism, and sclerodermic changes can appear. In the liver, a spectrum of histological changes can be found, including steatosis, mild to severe inflammation, fibrosis, and cirrhosis. Diagnosis of PCT is made on the basis of clinical suspicion and is confirmed by measuring increased levels of porphyrin in urine and, if available, direct measurement of the UROD enzyme activity. Treatment consists of avoiding precipitating factors (sun, alcohol, estrogens) and, if necessary, lowering iron overload (venipuncture) as well as treating HCV infection in affected patients. In general, treatment of chronic HCV infection leads to the normalization of UROD enzymatic activity, levels of liver aminotransferase and urine porphyrin, as well as disappearance of skin changes.

Lichen planus is a chronic inflammatory disease of the skin and mucosa which can affect hair and nails and is characterized by pruritic papulae. These most often appear on the skin

of extremities, face, scalp, nails, and mucosa of the gastrointestinal and genitourinary tract. Lichen planus occurs in various chronic liver diseases, and anti-HCV antibodies can be found in 10–40% of patients with lichen planus [20]. It is assumed that the occurrence of lichen planus is immunologically mediated, but the exact mechanism is unknown. It is also considered a premalignant condition and is known to progress to squamous cell carcinoma. The treatment of HCV infection with interferon therapy did not result in regression of lichen planus in most studies; on the contrary, there are reports of appearance or exacerbation of lichen planus during interferon therapy. A recent case series involving seven patients with oral lichen planus treated with interferon-free protocols showed an improvement of symptoms without adverse events [21].

Leukocytoclastic vasculitis is associated with essential mixed cryoglobulinemia and is a consequence of blood vessel involvement. It is clinically characterized by palpable pruritic changes and petechiae which usually affect lower extremities and is treated as other manifestations of essential cryoglobulinemia.

Necrolytic acral erythema, a condition characterized by painful, pruritic, and erythematous skin lesions of extremities is reported to be strongly associated with chronic HCV infection. Zinc supplementation has been associated with improvement of the condition.

Some data supports a possible connection of chronic HCV infection with chronic pruritus, while sporadic reports also suggest an association of HCV infection with psoriasis, chronic urticaria, pyoderma gangrenosum, erythema nodosum, and erythema multiforme.

6. Ocular manifestations

Mooren's corneal ulcer represents a rare painful peripheral corneal ulceration, usually without accompanying scleritis. Some studies have made a connection between this rare form of corneal ulcer and chronic HCV infection, but the pathogenetic mechanism is not known [22]. Chronic HCV infection has been linked to other diseases of the eye such as sicca syndrome, keratitis, increased intraocular pressure, and episcleritis, while some disorders such as retinal bleeding, vision impairment, as well as rare cases of retinal artery or vein obstruction have been described as possible complications of interferon therapy.

7. Thyroid disorders

Thyroid disorders are relatively frequent in patients with chronic hepatitis C, especially in women. Antithyroid antibodies are, according to various reports, present in 5–17% (averaging at 10%) of patients with HCV infection, while thyroid diseases (mostly hypothyroidism) occur less often, in 2–13% of patients [23]. Thyroid function disorders appear even more often during interferon therapy, probably as a consequence of autoimmune activity precipitated by immunomodulatory therapy, but can persist even after treatment completion. There is some evidence of a possible HCV infection of thyroid tissue causing a local inflammatory response that might trigger the autoimmune process. In any case, determining thyroid hormones as well as

anti-thyroglobulin and antithyroid peroxidase antibodies is necessary in all HCV-infected patients, especially before and periodically during interferon therapy. Substitution therapy with thyroid hormones is used in hypothyroidism treatment. In cases of mild hyperthyroidism, symptomatic therapy is used, while thyrostatic therapy is reserved for more severe cases. Interferon therapy should be stopped in cases of severe hyperthyroidism caused by the treatment. It will be interesting to see how the eradication of HCV infection with new drug combinations without interferon affects thyroid function disorders in patients with chronic hepatitis C.

8. Sicca syndrome

The sicca syndrome develops in most patients with Sjögren's syndrome. Lymphocytic sialadenitis resembling Sjögren's syndrome has been described in patients with chronic HCV infection who complain of mouth or eye dryness in 20–30% of cases [15]. There are, however, histological (milder, mostly pericapillary lymphocytic infiltration without ductal destruction in HCV infection as opposed to periductal infiltration with destruction of excretory ducts in classic Sjögren's syndrome) and clinical differences (less pronounced symptoms, later onset, increased levels of serum cryoglobulin and RF, lower complement levels, positive antinuclear, and negative Ro/La antibodies). Therefore, it seems that HCV does not cause Sjögren's syndrome but rather symptoms that imitate it [14]. Treatment of chronic HCV infection leads to symptom resolution in patients with the sicca syndrome.

9. Other autoimmune manifestations

Various autoantibodies are frequently found in patients with chronic HCV infection. Rheumatoid factor (around 60%) is most often present followed by antinuclear antibodies (ANA, around 40%), antithyroid (35%), anticardiolipin (15%), and anti-smooth muscle antibodies (ASMA, around 7%), respectively. These antibodies appear in about one-half of patients with chronic HCV infection (40–65% according to different studies) but are commonly present in low titer and, for the most part, do not seem to affect the clinical course of the disease [1]. Antibodies to liver and kidney microsomes (anti-LKM-1) and actin are an exception and can be of clinical significance in some HCV-infected patients. These antibodies are usually characteristic for autoimmune hepatitis, and it has been noticed that, although patients with hepatitis C and anti-LKM-1 antibodies mostly benefit from interferon therapy, in some cases an increase in liver function tests can be observed. Some of these patients respond well to standard therapy for autoimmune hepatitis which consists of azathioprine and corticosteroids. Determining the primary cause of hepatitis in patients with overlapping HCV infection and autoantibodies can be very challenging, even though it has been shown that anti-LKM-1 antibodies in these patients are directed against different epitopes of cytochrome P450 2D6 compared to patients with autoimmune hepatitis [24]. Even though there are no recommendations for routinely determining the presence of these antibodies, if they are known to be present, greater caution during interferon therapy is recommended. The role of direct-acting antiviral drugs in these patients is yet to be determined.

Numerous studies have shown a connection between HCV infection and immune thrombocytopenic purpura (ITP) and/or hemolytic anemia, whether as a consequence of the infection itself or of interferon therapy. According to the results of one of the largest studies, it seems that chronic HCV infection is associated with a higher frequency of ITP in both treated and untreated patients, while increased risk of autoimmune hemolytic anemia was only present in patients treated with interferon therapy.

10. Musculoskeletal system

Arthralgia is common and reported by 40–80% of patients with chronic hepatitis C [1]. The joints are usually symmetrically affected, mostly knees and hands. The afflicted joints are painful, without deformities. True arthritis is rare, presenting as rheumatoid like arthritis in two-thirds and oligoarthritis in one-third of patients. Rheumatoid factor is present in 70–80% of patients with mixed essential cryoglobulinemia, but its presence does not correlate with joint affection [15]. Likewise, cyclic citrulline antibodies characteristic for rheumatoid arthritis are usually not present. Myalgia is also a common complaint. According to epidemiological studies, chronic HCV infection is associated with reduced bone mineral density and increased risk of fractures. The mechanism is probably linked to chronic inflammation and liver disease. Hepatitis C-associated osteosclerosis, mostly reported in patients with a history of intravenous drug abuse, is an uncommon disorder characterized by an increase in bone mass during adulthood. The increased bone turnover in periosteal, endosteal, and trabecular bone leads to the thickening of the skeleton and may respond to bisphosphonate or calcitonin therapy.

11. Neurological manifestations

Neurological manifestations of HCV infection can vary from central nervous system (CNS) involvement to peripheral neuropathy including sensorimotor neuropathy and mononeuritis multiplex. Evidence of CNS involvement includes the demonstration of HCV RNA in brain tissue and cerebrospinal fluid suggesting active replication and as well as a possible association of HCV infection and small vessel cerebrovascular disease [25–27]. The most common form of nerve involvement is distal sensory or sensorimotor polyneuropathy, which clinically presents with painful, asymmetric paresthesia, while multiple mononeuropathy occurs rarely [15]. These changes are a consequence of vasculitis, sometimes associated with cryoglobulinemia, involving vasa nervorum.

In a recently published study, chronic HCV infection has been linked to Parkinson's disease [28].

12. Neuropsychiatric disorders

Neurocognitive damages can manifest with a wide array of neuropsychiatric conditions, such as tiredness, depression, and lack of concentration and working memory, of which patients

with chronic HCV infection often complain. These disorders are often seen and intertwined with other associated conditions, such as chronic liver disease, cirrhosis, the use of drugs, and others. Some studies have managed to show that these neurocognitive damages are a consequence of the HCV infection itself, regardless of comorbidities [29]. Functional imaging methods have shown metabolic changes in brains of chronic hepatitis C patients, with improvement of cognitive function and brain metabolism observed after treating the HCV infection [30]. Some of these disorders such as depression and fatigue are important because they can exacerbate under interferon therapy. This is why it is important to perform mental status evaluation at the beginning and during this therapy, so as to be able to timely act with suitable psychiatric support, antidepressants, and anxiolytics. Fatigue, depression, and cognitive damage significantly impair functional ability (at work and at home) and impact the quality of life of patients with chronic HCV infection, while the eradication of the virus positively correlates with an improvement in quality of life.

13. Metabolic manifestations: diabetes mellitus and insulin resistance

Disturbed glucose metabolism, onset of insulin resistance (IR), and type 2 diabetes mellitus (T2DM) are often associated with chronic HCV infection. A meta-analysis of 34 studies confirmed a positive correlation between HCV infection and risk of T2DM, which is 1.7 times greater than the general population and notably increased compared to chronic hepatitis B patients [31]. It appears that the risk of T2DM in patients with chronic HCV infection is increased in patients with risk factors such as older age, obesity, advanced liver fibrosis, and a family history of diabetes [32]. Likewise, results of multiple studies have shown that successful eradication of HCV infection decreases IR and that the risk of T2DM is decreased in patients who achieved SVR [33]. Multiple studies have confirmed an association between the HCV infection and IR development that can be present without manifest T2DM. Experimental studies have shown that HCV causes significant changes in the lipid and glucose metabolism and that it leads to IR in the liver and peripheral tissue through direct (immediate influence of HCV proteins on intracellular insulin signal pathways) and indirect (the influence of TNF- α and other cytokines on the development of peripheral IR) mechanisms. Insulin resistance causes a series of changes in lipid and lipoprotein metabolism and leads to the development of liver steatosis [34]. Clinical implications of HCV-induced IR, besides T2DM development, include a worse response to interferon therapy, accelerated fibrosis and development of cirrhosis, increased risk of hepatocellular carcinoma, as well as increased cardiovascular morbidity and mortality [35].

14. Cardiovascular disease

Chronic HCV infection has been associated with accelerated atherosclerosis [36]. Risk of early carotid artery atherosclerosis (determined by intima-media thickness measurement) was four times greater in HCV patients than noninfected patients [14, 37]. In several cohorts of HCV-positive patients, increased cardiovascular mortality (1.5–25 times) as well as a higher

incidence of cerebrovascular and acute coronary syndromes was noted [38]. Besides coronary and cerebrovascular disease, an increased rate of peripheral arterial disease in patients with a chronic HCV infection has been described. Rates of acute coronary syndrome and ischemic stroke were significantly reduced in patients treated with peginterferon and ribavirin compared to untreated patients [39]. Although this association was found in studies originating from Far East countries, Western European and American studies, as well as a recent meta-analysis, have not established a clear correlation of HCV infection and increased cardiovascular and cerebrovascular risk [40, 41]. Likewise, the pathogenetic mechanism through which HCV leads to accelerated atherosclerosis has not been fully elucidated. There is evidence of HCV RNA presence in carotid plaques and endothelial cells in the brain, and it is possible that local infection leads to tissue damage, but atherosclerosis is more probably a consequence of the aforementioned IR, metabolism disturbance, and proinflammatory cytokine action. Many unsolved questions leave space for further research, and the arrival of new therapies opens new possibilities in treating patients with an expected decrease in cardiovascular morbidity and mortality.

15. Other HCV infection-associated diseases

Pulmonary fibrosis is a disease characterized by interstitial inflammation with focal fibroblast proliferation and collagen deposits leading to fibrosis, which clinically commonly manifests as dyspnea on exertion and nonproductive cough. The disease pathogenesis is unknown, and several studies have found a connection between pulmonary fibrosis and chronic HCV infection. A higher prevalence of pulmonary fibrosis was seen in HCV-infected patients than control groups, and vice versa, a group of patients with diagnosed idiopathic pulmonary fibrosis had an increased anti-HCV positivity rate (25%) [38].

Myasthenia gravis was associated with HCV infection in case reports only, and a clear link has not been established. Cases of this disease developing during interferon treatment have been described, but it is assumed that these cases were in fact exacerbations of subclinical disease precipitated by immunomodulatory therapy.

16. Conclusion

Chronic hepatitis C infection (HCV) is a systemic disease which, besides the liver as its primary target, affects a number of other organs and organ systems. So far more than 30 different conditions have been associated with chronic HCV infection. In general, the appearance of extrahepatic manifestations of HCV infection is unpredictable, that is, independent of the stage of the liver disease. A clear association with chronic hepatitis C has been established for many of these conditions, while, for some diseases, good-quality evidence linking them to HCV infection is still missing.

Considering the appearance of new direct-acting antiviral therapies that offer an excellent prospect for cure of infected patients, although at a relatively high expense, the practice in

Croatia, as well as in many economically limited countries, is to set treatment priorities, so as to sooner treat the patients that need it most. Taking this into regard, patients with established extrahepatic manifestations of HCV infection have priority in receiving treatment, regardless of the stage of their liver disease, as stated in the latest guidelines.

For example, patients with essential mixed cryoglobulinemia and its skin (leukocytoclastic vasculitis), kidney (membranoproliferative glomerulonephritis or membranous nephropathy, renal failure), or nerve (neuropathy) manifestations, as well as patients with non-Hodgkin lymphoma, porphyria cutanea tarda, and some other more rare autoimmune disease manifestations, will benefit from treatment not only by eradicating HCV but also in treating the extrahepatic manifestation and its sometimes very debilitating symptoms.

It can be expected, and recent studies show promising results, that new therapies without interferon which greatly improve therapeutic success with fewer adverse effects will prove especially beneficial in patients with immunologically mediated extrahepatic manifestations.

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References

- [1] Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine interne et maladies Infectieuses sur le virus de l'Hepatite C Medicine. 2000;**79**:47-56
- [2] Cacoub P, Poynard T, Ghillani P, et al. Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. Arthritis Rheum. 1999;**42**:2204-2212
- [3] European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. Journal of Hepatology. 2017;**66**:153-194
- [4] Ministry of Health Referral Centre for Diagnosis and Treatment of Viral Hepatitis. Hepatitis C Treatment Recommendations. Available from: www.bfm.hr/page/hepatitis-c [Accessed: Sep 8, 2017]

- [5] Lunel F, Musset L, Cacoub P, et al. Cryoglobulinemia in chronic liver diseases: Role of hepatitis C virus and liver damage. *Gastroenterology*. 1994;**106**:1291-1300
- [6] Dedania B, Wu GY. Dermatologic Extrahepatic manifestations of hepatitis C. *Journal of Clinical and Translational Hepatology*. 2015;**3**:127-133
- [7] Gagnani L, Fognani E, Piluso A, et al. Long-term effect of HCV eradication in patients with mixed cryoglobulinemia: A prospective, controlled, open-label, cohort study. *Hepatology*. 2015;**61**:1145-1153
- [8] Saadoun D, Thibault V, Si Ahmed SN, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. *Annals of the Rheumatic Diseases*. 2016;**75**:1777-1782
- [9] Gagnani L, Visentini M, Fognani E, et al. Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. *Hepatology*. 2016;**64**:1473-1482
- [10] Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: Systematic review and meta-analysis. *Gastroenterology*. 2003;**125**:1723-1732
- [11] Giordano TP, Henderson L, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. *Journal of the American Medical Association*. 2007;**297**:2010-2017
- [12] Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: Epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. *Blood*. 2011;**117**:1792-1798
- [13] Kawamura Y, Ikeda K, Arase Y, et al. Viral elimination reduces risk of lymphoma in patients with hepatitis C. *The American Journal of Medicine*. 2007;**120**:1034-1041
- [14] Tang L, Marcell L, Kottitil S. Systemic manifestations of hepatitis C infection. *Infectious Agents and Cancer*. 2016;**11**:29
- [15] Cacoub P, Comarmond C, Domont F, et al. Extrahepatic manifestation of chronic hepatitis C virus infection. *Therapeutic Advances in Infectious Disease*. 2016;**3**:3-14
- [16] KDIGO (Kidney Disease: Improving Global Outcomes). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl*. 2008;**109**:1-99
- [17] Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in porphyria cutanea tarda: Systematic review and meta-analysis. *Journal of Hepatology*. 2003;**39**:620-627
- [18] Garcovich S, Garcovich M, Capizzi R, et al. Cutaneous manifestations of hepatitis C in the era of new antiviral agents. *World Journal of Hepatology*. 2015;**7**:2740-2748
- [19] Dedania B, Wu GY. Dermatologic extrahepatic manifestations of hepatitis C. *Journal of Clinical and Translational Hepatology*. 2015;**3**:127-133

- [20] Gumber SC, Chopra S. Hepatitis C: A multifaceted disease. Review of extrahepatic manifestations. *Annals of Internal Medicine*. 1995;**123**:615-620
- [21] Nagao Y, Kimura K, Kawahigashi Y, et al. Successful treatment of hepatitis C virus-associated oral lichen planus by interferon-free therapy with direct-acting antivirals. *Clinical and Translational Gastroenterology*. 2016;**7**:e179
- [22] Wilson SE, Lee WM, Murakami C, et al. Mooren's Corneal ulcers and hepatitis C virus infection. *The New England Journal of Medicine*. 1993;**329**:62
- [23] Antonelli A, Ferri C, Pampana A, et al. Thyroid disorders in chronic hepatitis C. *The American Journal of Medicine*. 2004;**117**:10-13
- [24] Muratori L, Lenzi M, Ma Y, et al. Heterogeneity of liver/kidney microsomal antibody type 1 in autoimmune hepatitis and hepatitis C virus related liver disease. *Gut*. 1995;**37**:406-412
- [25] Weissenborn K, Krause J, Bokemeyer M, et al. Hepatitis C virus affects the brain-evidence from psychometric studies and magnetic resonance spectroscopy. *Journal of Hepatology*. 2004;**41**:845-851
- [26] Laskus T, Radkowski M, Bednarska A, et al. Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. *Journal of Virology*. 2002;**76**:10064-10068
- [27] Morgello S, Murray J, Van Der Elst S, et al. HCV, but not HIV, is a risk factor for cerebral small vessel disease. *Neurology: Neuroimmunology & NeuroInflammation*. 2014;**1**:27
- [28] Tsai HH, Liou HH, Muo CH, et al. Hepatitis C virus infection as a risk factor for Parkinson disease: A nationwide cohort study. *Neurology*. 2016;**86**:840-846
- [29] Monaco S, Mariotto S, Ferrari S, et al. Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015. *World Journal of Gastroenterology*. 2015;**21**:11974-11983
- [30] Byrnes V, Miller A, Lowry D, et al. Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. *Journal of Hepatology*. 2012;**56**:549-556
- [31] White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: A systematic review and meta-analysis. *Journal of Hepatology*. 2008;**49**:831-844
- [32] Petit JM, Bour JB, Galland-Jos C, et al. Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C. *Journal of Hepatology*. 2011;**35**:279-283
- [33] Aghemo A, Prati G, Rumi M, et al. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. *Hepatology*. 2012;**56**:1681-1687
- [34] Kralj D, Virović Jukić L, Stojsavljević S, et al. Hepatitis C virus, insulin resistance, and steatosis. *Journal of Clinical and Translational Hepatology*. 2016;**4**:66-75

- [35] Adinolfi LE, Restivo L, Zampino R, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. *Atherosclerosis*. 2012;**221**:496-502
- [36] Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T, Hepatitis C. Virus and atherosclerosis in patients with type 2 diabetes. *Journal of the American Medical Association*. 2003;**289**:1245-1246
- [37] Domont F, Cacoub P. Chronic hepatitis C virus infection, a new cardiovascular risk factor? *Liver International*. 2016;**36**:621
- [38] Gill K, Ghazinian H, Manch R, Gish R. Hepatitis C virus as a systemic disease: Reaching beyond the liver. *Hepatology International*. 2016;**10**:415-423
- [39] Adinolfi LE, Zampino R, Restivo L, et al. Chronic hepatitis C virus infection and atherosclerosis: Clinical impact and mechanisms. *World Journal of Gastroenterology*. 2014;**20**:3410-3417
- [40] Hsu YC, Ho HJ, Huang YT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut*. 2015;**64**:495-503
- [41] Wong RJ, Kanwal F, Younossi ZM, et al. Hepatitis C virus infection and coronary artery disease risk: A systematic review of the literature. *Digestive Diseases and Sciences*. 2014;**59**:1586-1593