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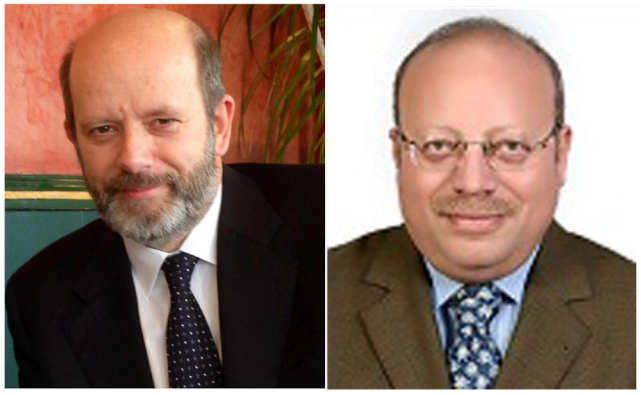
EDITORIAL

# Extrahepatic manifestations in hepatitis C virus infection



HCV infection is a major cause of chronic liver disease worldwide, ultimately leading to cirrhosis and hepatocellular carcinoma. Globally, it is estimated that up to 185 million people have been infected with HCV [1], and among these, according to the World Health Organization, ~130–150 millions are chronically infected [2]. Recent estimates place to ~700,000 the yearly death toll of liver-related, long-term sequelae of HCV [3]. In many regions of the world, where access to therapy is available, the number of deaths due to HCV has even surpassed that due to HIV infection [4]. Antiviral therapy is available for HCV, with success rates currently above 95%. A sustained virological response (SVR; undetectable HCV RNA 12 or 24 weeks after the end of therapy) is associated with improved clinical outcomes, and large studies have shown that treatment of chronic hepatitis C with antivirals decreases the risk of liver-related mortality [5–8].

HCV infection is also associated with several extra-hepatic manifestations, which add to the morbidity and mortality burden of HCV. Patients infected with HCV may develop, among many other disorders, mixed cryoglobulinemia, insulin resistance, several cardiovascular diseases, fatigue, depression, and cognitive impairment, translating into a significant public health impact in terms of both direct and indirect costs [9,10]. The pathogenesis of the extra-hepatic features of HCV is not always clear and may involve endocrine effects, direct toxic effects due to HCV replication in extra-hepatic tissues, or disproportionate immune reactions with systemic effects.

According to a recent meta-analysis [10], the most frequent extrahepatic manifestation occurring in HCV infected persons is depression, with a pooled prevalence of 24.5% vs. 17.2% in uninfected controls. Hepatitis C patients have a risk for developing depression of 2.30 vs. persons without HCV. This finding alone underlines the public health impact of extrahepatic manifestations of hepatitis C: depression is associated with a high rate of mortality and health resource use, with estimated annual direct costs, for the US, of USD 430.7 million USD [10]. Another major manifestation is represented by type 2 diabetes. The pooled prevalence of diabetes in hepatitis C patients has been estimated at 15%, compared with 10% in the uninfected population, with a pooled odds ratio for diabetes of 1.58 vs. controls [10]. According to the same study, the yearly direct costs associated with the management of diabetes in HCV-infected persons are even higher than those calculated for depression, and total to about 443 million USD per year. Mixed cryoglobulinemia (MC), which is probably the best known extrahepatic syndrome associated with HCV, affects as many as 30.1% of HCV-infected persons, vs. 1.9% of uninfected controls (with a risk ratio of about 12), but the prevalence of symptomatic MC is much lower, i.e. 4.9% (vs. 0% in controls) [10]. This is nonetheless significant from the clinical standpoint, because MC may lead to severe, life-threatening complications, such as glomerulonephritis, renal insufficiency and B-cell lymphoma. HCV has also notable effects on the health-related quality of life and other patients' reported outcomes, impacting both physical and psychical well-beings, with fatigue being significantly increased with respect to uninfected controls. Thus, overall, the public health burden of extrahepatic manifestations associated with HCV is a major one, as underlined by the total estimated annual direct costs of 1506 million USD for the US alone, a figure where

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indirect costs – such as those linked to decreased productivity at work – are not even considered.

A sizable proportion of the costs linked to HCV can be offset by viral eradication. A prospective cohort study reported that patients with chronic HCV infection have an increased risk of death from both liver- and non-liver-related diseases, including cardiovascular and renal diseases, compared to uninfected persons and those with anti-HCV but undetectable HCV RNA [7]. Importantly, a multicenter study has shown that curing HCV with antivirals reduces both liver-and non-liver-related mortalities [8]. Studies focusing on single extrahepatic manifestations have provided convincing evidence in favor of the benefits of viral clearance. Thus, SVR is associated with reduced levels of insulin resistance and risk of type 2 diabetes, and resolution of most MC-related complications, including the remission of some forms of HCV-associated B-cell lymphoma, reduced incidence of stroke and other cardiovascular outcomes (especially in the presence of diabetes), and improved patients' reported outcomes such fatigue and health-related quality of life [9].

Thus, it is not surprising that regulatory agencies around the world have recently approved costly antivirals for treatment of patients with clinically significant extrahepatic manifestations, independently of the stage of liver disease. The advent of well-tolerated interferon-free treatment regimens has increased the number of patients eligible for therapy, extending the access to treatment to those in whom interferon was contraindicated, e.g. because of uncontrolled depression, severe fatigue, autoimmune disorders and cardiovascular diseases.

This special issue focuses on some of the most clinically relevant extrahepatic manifestations of HCV infection, with a detailed discussion on the epidemiology, pathogenesis and management, written by leading experts in the field. We trust that it will increase the appreciation of these important clinical syndromes for whom appropriate management is now available.

Proper understanding of the pathogenesis of HCV infection and its effects on organs other than the liver are improving. This leads to the rise of attention to chronic HCV infection and its relation to the body systems and effect on the immunity [11]. Physicians other than hepatologists should be aware about the role of HCV infection and its extrahepatic effects helping the diagnosis of unexplained manifestations as arthralgia and unexplained fatigue [12].

The awareness about HCV infection, mode of transmission and clinical presentations is rising among the population. The link between unexplained presentations and HCV infection becomes more understandable within the community. The improvement of knowledge is attributed to the media, healthcare providers and contact to infected persons with HCV [13,14].

The availability of potent, effective treatment encourages the treatment of chronic HCV especially with the presence of specialized centers for treatment of the disease and related complications with affordable cost on the national and private bases. The effect of the recent drugs used for treatment of HCV should be studied more deeply on the improvement of extrahepatic manifestations of HCV after viral clearance [15].

## Conflict of Interest

*The authors have declared no conflict of interest.*

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