Treatment of Extrahepatic Manifestations of Hepatitis C Virus

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KEYWORDS

• Direct-acting antivirals • Sofosbuvir • IFN-free regimens • Cryoglobulinemia • Lymphoma • HCV • Chronic kidney disease • Lichen planus

KEY POINTS

- Antiviral treatment has been shown to prevent many non-liver-related complications and reduce all-cause mortality in patients infected with HCV, because anti-HCV therapy improves virus-related extrahepatic manifestations (EHMs).
- Antiviral treatment of patients suffering from mixed cryoglobulinemia syndrome (MCS) and non-Hodgkin lymphoma (NHL) is able to achieve clinical response of vasculitis-related manifestations and hematologic disease remission, so it should be considered a first-line treatment option in these patients.
- Extrahepatic benefits of antiviral therapy include improvement of HCV-related chronic kidney disease (CKD) and cutaneous manifestations, prevention of type 2 diabetes development and cardiovascular risks, together with improved quality of life and neurocognitive functions.
- Development of IFN-free regimens allows large-scale treatment of patients suffering from EHMs, by providing safe and efficacious options for patients previously IFN contraindicated.

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INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is now considered a systemic disease, because HCV-related extrahepatic manifestations (EHMs) have been shown to affect whole-organ functioning through multiple disorders. Better knowledge of HCV-associated diseases has led to understand that antiviral treatment represents a true etiologic therapy for some EHMs and, most of all, is able to prevent development of several non-liver-related complications. Recently, many studies have demonstrated that HCV clearance is associated with improved survival independently from liver-related outcomes: indeed the achievement of a sustained virologic response (SVR) to antiviral treatment has been associated with reduction of all-cause mortality in many large population studies.[1,2] Moreover, a Taiwanese study, including 12,384 patients with HCV receiving antiviral therapy matched with 24,768 untreated control subjects, showed that HCV treatment is associated with improved extrahepatic outcomes, such as lower incidence of end-stage renal disease, acute coronary syndrome, and ischemic stroke.[3]

Consequently, SVR is now regarded as a relevant survival end point also in patients with HCV with milder liver disease. Although anti-HCV treatment of patients suffering from EHMs was not systematically pursued in the past, because of reduced efficacy and high rates of adverse events typical of interferon (IFN)-based regimens, availability of potent and safe direct-acting antivirals (DAAs) has paved the way to large-scale treatment also in these patients. This article summarizes current data concerning antiviral therapy of common HCV-related EHMs.

MIXED CRYOGLOBULINEMIA

Since the demonstration that HCV infection is responsible for immune complexes formation in mixed cryoglobulinemia (MC), antiviral treatment has become one of the mainstays for treating MC-related vasculitis. Reports about successful MC treatment date back to the IFN-based therapy, which was shown to improve vasculitic manifestations in most patients. Several studies consistently demonstrated the strong link between virologic response, serologic response (decrease in serum cryocrit, rheumatoid factor negativization, normalization of C4 complement fraction levels), and clinical response (improvement in MC-related vasculitic manifestations): indeed nearly all patients achieving the SVR also showed improved biochemical profile and clinical symptoms, and conversely, virologic relapse with onset of viral replication resulted in MC recurrence.[4–8] However, SVR rates were still suboptimal (48%–60%) because of low efficacy of pegylated (Peg) IFN plus ribavirin (Rbv) therapy, and most studies were retrospective or lacked adequate follow-up.

An Italian study tried to prospectively evaluate long-term outcomes of viral eradication in MC, by comparing 121 patients with HCV with symptomatic MC (MC syndrome [MCS]), 132 asymptomatic patients with MC, and 158 patients with HCV without cryoglobulins treated with PegIFN plus Rbv, with a mean follow-up of 92.5 months. SVR was achieved by 52% of patients in the MCS group, and was associated with a persistent clinical and serologic response in all but two patients. On the contrary, non-SVR patients were also clinical nonresponders, although transient improvement of MCS was observed concomitantly to viremia decreasing on-therapy. Surprisingly, patients from MC and MCS groups showed lower SVR rates compared with the HCV group without MC (49% vs 61%; $P = .01$), despite similar viral kinetics on-treatment.[9] Reduced SVR in patients with MC could not be linked to higher treatment discontinuation rates for adverse events, although patients with MCS experienced more side effects than the HCV control group, mostly anemia and neutropenia. It has been