Review

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Evidence-based recommendations on the management of extrahepatic manifestations of chronic hepatitis C virus infection

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Key point

The objective of this international consensus is to provide therapeutic recommendations for HCV patients with extrahepatic manifestations.

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Introduction

The hepatitis C virus (HCV), a linear, single-stranded RNA virus identified in 1989, is a hepatotropic virus that causes liver cirrhosis and hepatocellular cancer and is a global health problem. It is recognized as one of the hepatic viruses most often associated with the development of extrahepatic manifestations (EHMs), which can be classified according to the principal underlying etiopathogenic process (autoimmune, inflammatory, metabolic or neoplastic) [1]. HCV infected patients with extrahepatic involvement require a multidisciplinary approach and a complex therapeutic management.

In the 1990s, various authors described the association between HCV infection with organ damage beyond the liver and a heterogeneous group of extrahepatic conditions including pulmonary fibrosis, cutaneous vasculitis, glomerulonephritis, Mooren ulcer, porphyria cutanea tarda and lichen planus, among others [2–4]. However, it is currently accepted that there is a weak association with some of these features [1,5], and that cryoglobulinemic vasculitis (CV) is the key extrahepatic disease related to chronic HCV infection. There is growing interest in the association with both systemic and organ-specific autoimmune diseases and with the development of neoplastic haematologic processes due to the specific lymphotropism of HCV [1,6,7].

Currently, there are no international recommendations on the therapeutic management of HCV infected patients with EHMs. The first therapeutic approaches were based on immunosuppressive therapies mirroring the regimens used in non-HCV vasculitides [8]. The introduction of the first antiviral therapies combination (interferon [IFN] alpha and ribavirin [RBV]) clearly improved survival rates[9]. However, this therapeutic approach had limited virological efficacy (eradication <50% for HCV genotype 1), often required several months of therapy and had high rates of intolerance [10]. Direct-acting antiviral (DAA) therapies have recently emerged as a striking therapeutic approach for HCV infection, with a short treatment duration, minimal side effects and efficacy approaching 100% [11–14]. These new drugs are providing the opportunity to effectively cure chronic HCV infection and reduce the burden caused by both the hepatic and extrahepatic complications of HCV, thereby offering hope for a dramatic change in patient outcomes. The objective of this international multidisciplinary consensus is to provide the first set of recommendations on a homogeneous therapeutic approach to HCV infected patients with extrahepatic involvement in the new DAA era.

Methods

In 2015, the convenor (PC) and co-convenors (MC, CF, PL, AM, MRC, DS, AT, ZY, ALZ) constituted the Steering Committee of the International Study Group of Extrahepatic Manifestations related to HCV (ISG-EHCV). International experts known for their experience in managing and treating HCV infected patients and their long, active history of clinical/basic research in this field were invited to join the multidisciplinary Advisory Working Group, including rheumatologists, internists, hepatologists, nephrologists and haematologists. To find potential topics of interest related to the therapeutic management of EHM, a core group (MRC, ALZ, CF and PC) created a list of potential proposals (no limit were placed on proposals) (Table S1), which were categorized, refined (overlapping questions were eliminated) and grouped in to three categories: A)

Antiviral therapeutic approach; B) Pre-treatment evaluation; and C) Non-antiviral therapeutic approach. The specific search terms for the systematic literature review (SLR) for each proposal were also discussed. The SLR was carried out by MRC, PBZ and SR searching PubMed (July 20, 2016) using the following as key terms; "Hepatitis C virus", "extrahepatic" and "therapy", and as secondary terms those proposed for each specific statement, with no research restrictions. Other databases, such as EMBASE and Cochrane Library were also checked. Studies were considered as eligible when (i) the study population included adults with HCV chronic infection presenting EHMs; (ii) the intervention consisted of therapy with specific drugs; (iii) studies were randomized controlled trials, prospective cohort, retrospective cohort, case-control studies and case series; isolated case reports were accepted only for DAA regimens; reviews, experimental animal studies, *in vitro* studies and duplicate publications were excluded; and (iv) studies contained sufficient and clear information about the effect of the drugs evaluated (antiviral and non-antiviral) on the extrahepatic manifestations presented by the patients, either classified as improvement *vs.* no improvement, or as complete response, partial response or no response. In addition, the current evidence-based guidelines for the therapeutic management of unselected HCV infected populations were also specifically evaluated, including the UK 2014 [15], Latin American Recommendations [16], INASL Recommendations 2015[17], EASL 2016 [18] and the AASLD/IDSA 2015 [19].

Based on the SLR results, a core group (MRC, ALZ, CF and PC) developed initial statements and a support group (PBZ, SR) prepared and reviewed the scientific evidence to support each statement/recommendation. The approved set of preliminary recommendations was sent online to the entire ISG-EHCV group according to the Delphi method [20]. A web-based Delphi procedure using Google Forms was carried out to reach consensus on the proposed statements and the subsequent proposed recommendation. Each proposal was graded according to priority (4 = high, 3 = moderate, 2 = low, 1 = no priority) and the level of agreement on a 0–10 scale (0, no agreement; 10, full agreement). In the first Delphi round, we excluded propositions scored as high priority by less than 80% of participants and those which did not reach a mean agreement score of at $\geq$5. Proposals scored as high priority with a mean agreement score of >9 were automatically endorsed. When the initial mean agreement score ranged between 5 and 9, the contents or wordings were amended and sent to subsequent Delphi rounds until a mean score of >9 was achieved. An ultimate round of wording refinements was carried out online but with no changes in the meaning permitted. Table S2 summarizes the scores achieved in the two Delphi rounds finally carried out. The level of scientific evidence was classified on a 5-point scale and the strength of evidence on a 3-point scale [21] (Tables S3 and S4).

Summary of evidence

The current armamentarium against HCV has been expanded in the last 5 years with an explosion of new molecules able to directly target non-structural proteins that play a key role in HCV replication (Fig. 1). These agents have been called DAAs [22] and target some of the main molecular components of HCV, including NS3/4A protease (first and second generation protease inhibitors), NS5B polymerase (nucleoside and non-nucleoside analogs) and NS5A protein. In spring 2011, the US Food and Drug Administration (FDA) approved the first generation of NS3/4A protease inhibitors (boceprevir and telaprevir) as treatments for chronic HCV infection. NS3/4A protease inhibitors (PIs: telaprevir, boceprevir, simeprevir, paritaprevir, voxilaprevir, asunaprevir, grazoprevir, glecaprevir) block the catalytic site of the protease, resulting in the failure of polyprotein cleaving and processing. NS5B polymerase inhibitors include nucleoside analogs (sofosbuvir) that act as chain terminators within the polymerase catalytic site and non-nucleoside inhibitors (dasabuvir, beclabavir) bind to different allosteric sites causing conformational changes that render the polymerase ineffective. Finally, NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, velpatasvir, elbasvir, pibrentasvir) have been shown to be potent antivirals, although the exact mechanism by which they interact with the NS5A protein and inhibit HCV replication remains unclear [22]. Table 1 summarizes the main results obtained by the different antiviral therapeutic regimens [23–54]. In addition to the new generation of antiviral therapies, biological therapies targeting B cells (rituximab) have increasingly been used in HCV-induced cryoglobulinaemia vasculitis [55].

Since 2014, 8 studies (4 isolated case reports, 1 case series, 1 retrospective and 2 prospective studies) have reported the use of DAA in combination with pegylated IFN (PegIFN) + RBV in 50 patients with EHMs (all but two had HCV-related CV) (Table 2). DAAs mainly included first generation NS3/4A protease inhibitors (boceprevir in 21 cases, telaprevir in 20). With respect to IFN-free DAA regimens, since 2015 11 studies (6 isolated case reports, 1 case series, 2 retrospective and 2 prospective studies) have reported the use of DAAs without IFN in 120 patients with EHMs (all but five had HCV-related CV) (Table 3): 59 patients were treated with RBV-containing DAA regimens (Table 3a) and 61 with RBV-free DAA regimens (Table 3b).

B cell depletion with rituximab is the most promising biologic approach to cryoglobulinaemia employed to date. The principle underpinning the

Key point

The current therapeutic armamentarium against HCV has been recently expanded with an explosion of new molecules (DAAs) with high virological efficacy.

Key point

B cell depletion with rituximab is the established biologic approach to cryoglobulinaemic vasculitis (CV) employed to date.

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