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

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LAY SUMMARY

- The current therapeutic armamentarium against HCV has been recently expanded with an explosion of new molecules (DAAs) with high virological efficacy
- The objective of this international consensus is to provide therapeutic recommendations for HCV patients with extrahepatic manifestations (EHM).
- The use of non-antiviral therapeutic approaches should be evaluated according to the type of EHM and severity of the clinical presentation
- B cell depletion with rituximab is the established biologic approach to cryoglobulinaemic vasculitis (CV) employed to date.
- The efficacy of therapies in EHM patients should be evaluated not only according to the virological response, but also according to the full impact of the other clinical and immunological responses achieved.
- Clinical experience of the use of the new DAAs in EHM remains very limited, with less than 100 cases reported in the last 2 years (overwhelmingly in CV patients)

1. 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, 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 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 hematologic 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 extrahepatic manifestations (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 alpha and ribavirin) 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.

2. 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) (**Supplementary Table 1)** which were categorized, refined (overlapping questions were eliminated) and grouped in 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 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 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 ≥ 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 on-line but with no changes in the meaning permitted. **Supplementary Table 2** 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] (**Supplementary Tables 3 and 4)**.

3. 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 (**Figure 1**). These agents have been called direct-acting antiviral agents (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 pIFN + RBV in 50 patients with

EHMs (all but two had HCV-related cryoglobulinemic vasculitis -CV-) (**Table 2**). DAAs included mainly 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 DAA without IFN in 120 patients with EHMs (all but five had HCV-related CV) (**Table 3**): 59 patients were treated with ribavirin-containing DAA regimens (**Table 3a**) and 61 with ribavirin-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 use of rituximab in cryoglobulinaemia is that peripheral B lymphocyte depletion should lead to a reduction in the B-cell clones that produce cryoglobulins. The first studies were published in 2003, and since then, 14 studies including nearly 400 patients have been reported, including 1 retrospective study, 7 prospective studies, 3 case-control studies, 1 phase II trial and 2 RCTs (**Table 4**)[39–52].

4. RECOMMENDATIONS

A. ANTIVIRAL THERAPEUTIC APPROACH

Recommendation A1. Antiviral treatment is recommended for all patients with EHM, except those with limited life expectancy due to causes unrelated to HCV.

According to the recommendations of the 2015 AASLD/IDSA guidelines[18,19], current evidence clearly supports the use of antiviral therapy in all HCV infected persons, including those with EHMs. These guidelines included patients with CV or renal involvement in the subsets of patients with the highest priority for treatment as they had the highest risk of life-threatening complications. Evidence on the clinical efficacy of HCV eradication in patients with EHMs is solid, especially those with CV[1,7,55] and those with associated B-cell lymphoma[6,56], although it is overwhelmingly based on non-randomized, observational studies. As stated in the guidelines for the general HCV infected population[19], it is reasonable to exclude from this general recommendation patients with limited life expectancy (i.e. metastatic cancer) while, if the short life expectancy is related to EHMs, the etiologic treatment has the highest priority.

LEVEL OF EVIDENCE: 2 for CV and B-cell lymphoma; 3-5 for the remaining EHMs
LEVEL OF AGREEMENT: 9.1/10
STRENGTH OF RECOMMENDATION: B

Recommendation A2. DAA-based, IFN-free regimens (with or without ribavirin) should be considered the standard antiviral therapeutic approach in HCV-related EHM

Current evidence has clearly demonstrated the higher efficacy and lower rate of side effects of the new DAA-based, IFN-free regimens in comparison with the old IFN-containing regimens[57]. It is reasonable to consider *a priori* DAA-based, IFN-free regimens as the standard antiviral treatment for HCV infected patients with EHMs. The current evidence on the use of DAAs in EHMs is overwhelmingly centred on vasculitis, with 50 patients being treated with IFN-containing regimens and 120 with IFN-free regimens. Slightly more patients treated with IFN-containing regimens had a complete clinical response (76% vs. 68%) and cryoglobulin clearance rates (56% vs. 47%), with a clearly lower rate of SVR (68% vs. 92%) compared with patients treated with IFN-free regimens (**Table 1**). Caution on the interpretation of these data is warranted due to the large degree of heterogeneity in patient characteristics, the different DAA regimens used and the uncontrolled designs of the studies. The key factors supporting the use of IFN-free regimens in patients with EHMs should probably be the potential risk of development or worsening of autoimmune diseases due to IFN use and the significantly lower rate of adverse effects. **Table 5** summarizes the main side effects reported in EHMs patients in the main studies using DAAs. There was a significant difference in the rates of side effects between patients treated with IFN-containing regimens and those treated with IFN-free regimens: the frequency of all side effects but one (insomnia/irritability) was higher in patients treated with regimens containing IFN (for some side effects the frequency was 2-4-fold higher compared with IFN-free regimens). The rate of treatment discontinuation was higher in patients treated with IFN-associated regimens (27%, mainly due to lack of viral response, with one case of discontinuation associated with depression) compared to 8% of those treated with IFN-free regimens (due to irritation/hallucinations, worsening of anxiety and death unrelated to therapy).

With respect to the addition of RBV in IFN-free regimens, there were 59 reported patients with EHMs treated with DAA and RBV and 61 treated with RBV-free DAA regimens. Slightly more patients treated with RBV-containing regimens had a complete clinical response (74% vs. 64%), with a similar rate of cryoglobulin clearance (47% vs. 48%) and a lower rate of SVR (88% vs. 97%) compared with patients treated with RBV-free regimens (**Table 1**). Once again, these results should be interpreted with caution due to the great diversity and the uncontrolled nature of the data. Caution is warranted in managing anaemia related to RBV. RBV should not be given if baseline haemoglobin levels are < 10 g/dL[19], especially in EHMs associated with anaemia (severe autoimmune cytopenias, severe glomerulonephritis).

There is little specific information on the clinical efficacy of antiviral therapies on non-vasculitic autoimmune features (sicca features, arthritis, cutaneous lupus, pulmonary involvement…), and the results are controversial. Nissen et al[58] reported that the use of IFNa in HCV patients

with non-vasculitic features had no effect or was associated with worsening in 10/12 (83%) of patients with arthralgia, 5/5 (100%) of those with arthritis, 6/6 (100%) of those with sicca features, 5/7 (71%) of those with fatigue and 3/4 (75%) of those with myalgia. Isaacs et al[59] reported no significant improvement in sicca symptoms and the number of painful joints after treatment with pegIFN + RBV in 118 HCV patients, while Fadda et al[60] reported exacerbation of arthritis in 8/35 (23%) patients with HCV-related arthritis after receiving IFN therapy. However, Zuckerman et al[61] reported a complete response to IFN in 12/28 (44%) HCV infected patients with arthritis, although nearly half had associated cryoglobulinemia. Currently, there are no data that support a specific recommendation for patients with non-vasculitic autoimmune manifestations, and therapeutic decisions that largely mirror those for vasculitic features might be recommended.

LEVEL OF EVIDENCE: 2 for vasculitic features, 5 for non-vasculitic features
LEVEL OF AGREEMENT: 9.39/10
STRENGTH OF RECOMMENDATION: B

Recommendation A3. At present, DAA-based, IFN-free regimens should be used following the recommendations for individuals with HCV mono-infection in the current international guidelines

Although international guidelines are not based on complete awareness of the efficacy and safety of these regimens in patients with EHMs, it seems reasonable to follow their recommendations until more data are available [18,19]. This may be especially recommended with respect to the underlying liver disease (degree of liver fibrosis, presence of compensated or decompensated cirrhosis) and concomitant clinical situations (viral co-infections, transplant recipients). Therapy must be tailored according to these characteristics in a highly-specialised multidisciplinary scenario, integrating the different comorbidities related to liver, autoimmune, inflammatory, metabolic and neoplastic diseases on a case-by-case basis.

LEVEL OF EVIDENCE: 5
LEVEL OF AGREEMENT: 9.14/10
STRENGTH OF RECOMMENDATION: C

Recommendation A4. When considering a choice between DAA regimens that achieve similar rates of SVR, care providers and clinicians should take into account the potential side effects associated with the regimen in EHMs patients and not only the cost/effectiveness ratio.

Table 1 summarizes the current available data. There are three regimens with at least 25 reported patients: pIFN-RBV+BCP/TLP (n=41), RBV+SOF (n=48) and DCV/LDV+SOF (n=25). The

rates of complete clinical response were 74%, 77% and 68%, cryoglobulin clearance were 50%, 45% and 36%, and SVR were 63%, 85% and 96%, respectively. The data are not robust enough to make a solid recommendation on the choice of a specific DAA regimen for EHMs patients, and choices should be made on a case-by-case basis. However, it seems clear that the impact of side effects related to the use of IFN (and the associated lower rate of completing antiviral therapy) makes IFN-free regimens a first choice over IFN-containing regimens, while RBV-free regimens could be used as the first-choice for patients with EHMs presenting with haemoglobin levels < 10 g/dL. The reduced length of therapy compared with older options is a strong positive point with respect to safety issues in patients with EHMs. In addition, the decision of which DAA regimen to use may involve consideration of drug interactions between DAAs and concomitant medications[19].

LEVEL OF EVIDENCE: 3 for CV, 5 for other EHMs
LEVEL OF AGREEMENT: 9.29/10
STRENGTH OF RECOMMENDATION: C

Recommendation A5. If a lack of resources limits the ability to treat all patients with EHM immediately with DAA as recommended, then it is most appropriate to treat those presenting with more severe EHM involvements first.

Due to the international scope of these guidelines, their worldwide application must be ensured by taking into account the differences in health care resources between countries. Where a lack of resources limits the ability to treat all EHMs patients immediately as recommended, it is most appropriate to treat those at greatest risk of disease complications first. The already-existing international recommendations for treating HCV[18,19] state that the new treatments should be preferentially applied to the more severe HCV-infected patients, in which definition HCV patients with EHM should be included. However, it should consider that the best results in terms of sustained and complete clinical response are often obtained when viral eradication is achieved early. Nevertheless, an accurate assessment of the organ involvements and their potential life-threatening damage according to the classification proposed in **Box 1** is essential to assess the priority/urgency of antiviral treatment (and even its length) and the need for more intensive treatment by adding non-viral therapies. No studies are available that compare the results of current antiviral treatments graded by severity of EHMs.

LEVEL OF EVIDENCE: 5
LEVEL OF AGREEMENT: 9.1/10
STRENGTH OF RECOMMENDATION: C

Statement A6. In the case of limited resources, the priority for the immediate initiation of antiviral therapies in the following subsets of EHM patients was rated as follows (highest to lowest priority):

a) Patients with HCV-related vasculitis (i.e. cryoglobulinaemia)

The vast majority of studies of the use of antiviral therapies in extrahepatic HCV disease have been carried out in patients with CV, which is considered the prototype of systemic autoimmune disease associated with HCV, both for their frequency and potential life-threatening involvement[62]. Patients with chronic HCV infection rarely develop types of vasculitis other than cryoglobulinaemia. All reported studies show that vasculitic manifestations overwhelmingly improve after antiviral treatment (even in patients with partial virological responses) and often disappear, especially in patients with a sustained viral response[63].

PRIORITY = 2.96/3
LEVEL OF EVIDENCE = 3
STRENGTH OF RECOMMENDATION: B

b) Patients with B-cell neoplasms

A close association between HCV and B cell non-Hodgkin lymphomas (B-NHL) has been reported in the last 20 years. A review of the main studies that used combined IFN + RBV to treat B-cell lymphoma (mostly MALT and MZL) in 205 HCV patients showed a complete response of lymphoma in 115 (56%) patients, a partial response in 48 (23%) and no response in 42 (21%) patients[64]. In addition, a recent study found a favourable association between survival and antiviral therapy (pegIFN+RBV including 6 cases with associated PI) in 116 HCV infected patients with B-cell lymphoma, and especially in those with MZL, supporting the idea that antiviral therapy improves the outcomes of HCV-associated lymphoma[65]. However, the use of DAA-based regimens requires investigation as only recent isolated cases have been reported[24,30,35,36], and the development of highly aggressive mantle cell lymphoma in two HCV infected patients one month after starting antiviral therapy with sofosbuvir has been recently reported[66]. An unsolved question concerns the role of DAA therapy in patients with aggressive lymphomas (DLBCL) and in patients in remission after cytotoxic chemotherapy[56]. In the absence of solid data, treatment of low-grade lymphomas only with antiviral therapies may be recommended whereas more aggressive lymphomas would require the addition of chemotherapy/rituximab[64]. IFN-free antiviral regimens might be less effective than IFN-containing regimens in some patients with B-cell lymphoma, possibly due to the lack of

additional anti-proliferative activity of IFN, while the association of rituximab with DAA regimens could be more effective than isolated antiviral therapies.

PRIORITY = 2.84/3
LEVEL OF EVIDENCE = 3
STRENGTH OF RECOMMENDATION: C

c) Patients with associated rheumatic/autoimmune systemic diseases (i.e., Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus)

The most commonly reported rheumatic/autoimmune systemic diseases associated with chronic HCV infection are Sjögren syndrome (nearly half the cases), RA and SLE[67]. Very few studies have analysed the therapeutic benefits of antiviral therapies on HCV-associated autoimmune systemic diseases. Doffoel-Hantz et al[68] reported a better clinical response of sicca symptoms in HCV-associated Sjögren syndrome patients treated with combined IFNa + RBV compared with patients receiving only IFNa, although more than 50% of patients presented severe side effects. Chen et al[69] reported HCV reactivation caused by immunosuppressive therapies in 10/26 (38%) patients with SLE, with no increase in lupus activity after treatment with IFNa + RBV. In a case-control study in SLE patients, HCV infected patients showed higher prevalence of cryoglobulin without CV, and SLE by itself or treated with steroids did not worsen HCV infection[70]. Of note, the use of IFN has been also associated with the development of some autoimmune systemic diseases including lupus, Sjögren syndrome, rheumatoid arthritis, myositis and sarcoidosis[71–74], so it seems reasonable to prioritize the use of IFN-free regimens. Currently, there are no solid data that support a specific recommendation for patients with HCV-associated autoimmune systemic diseases, and therapeutic decisions that largely mirror those for CV might be recommended.

PRIORITY = 2.3/3
LEVEL OF EVIDENCE = 3
STRENGTH OF RECOMMENDATION: C

d) Patients with associated organ-specific autoimmune diseases (i.e., thyroiditis)

Patients with chronic HCV infection have a high frequency of some organ-specific autoimmune diseases, mainly autoimmune thyroiditis, but also non-cryoglobulinemic glomerulonephritis, idiopathic pulmonary fibrosis, and cutaneous diseases such as lichen planus and porphyria cutanea tarda. There is little data on the response of these diseases to antiviral therapies. Thyroiditis has mainly been linked to the use of IFN, mostly in patients with anti-thyroglobulin/thyroperoxydase antibody. For HCV-related autoimmune

cutaneous diseases, several studies have reported a poor response of porphyria cutanea tarda to IFNa[75,76], while Esmail et al[77] reported the successful use of low dose ribavirin in HCV infected patients with lichen planus or pemphigoid. No data are available on the use of DAA in other HCV-related organ-specific autoimmune or metabolic diseases.

PRIORITY = 1.8/3
LEVEL OF EVIDENCE = 4
STRENGTH OF RECOMMENDATION: C

e) Patients with non-specific general features (i.e., fatigue, chronic pain, fibromyalgia)

A large percentage of patients with chronic HCV infection present with general symptoms, such as fibromyalgia, chronic pain or chronic fatigue, which have a significant impact on the health related quality of life (HRQOL) of HCV patients. In patients treated with older therapeutic regimens, these symptoms were closely associated with the IFN administration. However, many studies have shown a higher frequency of these symptoms in untreated patients, and have suggested that reduced HRQOL ~~life~~ may be related to neurocognitive alterations directly associated with HCV infection, regardless of the stage of liver fibrosis or the HCV genotype. These manifestations typically occur in the absence of structural brain damage. However, some neuroimaging studies have reported brain metabolic changes[78]. Improvements in neuropsychological assessments in patients who achieved spontaneous or treatment-induced viral clearance suggest a direct or indirect pathogenic role for HCV itself in neuropsychiatric and neurocognitive disorders[79]. A systematic review by Spiegel et al[80] of HRQOL after antiviral therapy found that physical function only improved in patients who achieved SVR. However, some studies have found improvements independently of SVR, suggesting that viral clearance alone can achieve significant physiological changes[59,81–83] In the new DAA era, one study in patients with HCV-CV[33] has evaluated the impact of DAA therapies on HRQOL. The SF-36 physical status score improved significantly, with a mean change from baseline of +10% at week 24 and +14% at week 36, while the mental status score also improved, with a mean change from baseline of +4% at week 24 and +7% at week 36. Younossi et al[84] recently analysed the patients reported outcomes (PRO, i.e. SF-36, CLDQ-HCV, FACIT-F, and WPAI:SHP) data from multicenter multinational phase 3 clinical trials of sofosbuvir with and without IFN or RBV. PRO instruments were administered to subjects at baseline, during, and up to 24 weeks after treatment. The use of interferon- and RBV-free regimens for HCV showed better patients' experience and work productivity during treatment.

PRIORITY = 1.5/3
LEVEL OF EVIDENCE = 3

STRENGTH OF RECOMMENDATION: C

B. PRE-TREATMENT EVALUATION

Recommendation B1. Prior to starting treatment, the following evaluation should be done:

a. Full clinical history and examination

b. Laboratory tests

c. Measurement of EHM disease activity (when available)

Patients should be evaluated prior to starting therapy following the general recommendations included in current guidelines to determine the severity of liver disease[19], also including a specific evaluation to obtain an accurate diagnosis of EHMs and to classify severity of EHMs (**Box 2**) in order to allow a further evaluation of the response to therapy of the EHM-related clinical and laboratory features. In some cases, and for different reasons (mostly the cost of tests and their availability in the reference central laboratory), it may not be not possible to carry out all these evaluations.

LEVEL OF EVIDENCE: 5
LEVEL OF AGREEMENT: 9.48/10
STRENGTH OF RECOMMENDATION: C

Recommendation B2. HCV genotyping may be performed in all patients, whereas IL-28B genotyping is not a mandatory prerequisite and may be required on a case-to- case basis.

Current evidence on the influence of HCV genotypes in the therapeutic response to DAA-based regimens in EHMs is too limited to make solid recommendations and it seems reasonable to follow the recommendations of the general guidelines on this subject. Ideally, HCV genotypes can help the choice and length of the DAA regimen according to general HCV recommendations (before the arrival of pan-genotypic DAAs). HCV genotyping may be performed in all patients, but it will increase the logistic burden in the case of mass, national campaigns and a cost/benefit equation should be considered for each country. Available data on the real role of IL28B testing are not strong enough to recommend it in all cases.

The evidence on the influence of HCV genotypes and IL-28B genotypes on the clinical presentation and outcomes of EHMs is very limited. With respect to the influence of HCV genotypes in EHMs, to our knowledge only one study in patients with CV found that HCV patients with genotype 1 had a higher mean age at diagnosis of cryoglobulinaemia and a higher prevalence of cryoglobulinaemic features, especially vasculitic features[85]. With respect to IL-28B genotypes, some studies have suggested a beneficial role as a prognostic marker of antiviral response in CV patients treated with pegIFN-RBV[86] but there was not impact with DAAs. Sansonno et al[87] found the IL-28B C/C genotype associated with a higher

risk of cryoglobulinaemic nephropathy and B cell malignancies in HCV-positive patients with CV. There is no clear evidence to consider IL28B testing today in the scope of HCV EHMs.

LEVEL OF EVIDENCE: 5
LEVEL OF AGREEMENT: 9.33/10
STRENGTH OF RECOMMENDATION: C

C. NON-ANTIVIRAL THERAPEUTIC APPROACH

Recommendation C1. Non-antiviral therapeutic approaches should be evaluated according to the type of EHM and severity of the clinical presentation

The non-antiviral therapeutic approaches mainly used in EHMs patients include glucocorticosteroids (GC), immunosuppressant agents (IA), plasma exchange and biological therapies. These non-antiviral approaches, mainly used in CV, were derived primarily from strategies employed in other systemic vasculitides before it was understood that most cases result from HCV infection

Non-antiviral therapeutic approaches are recommended for moderate and, especially, for severe organ-specific involvements (**Box 1**). Patients with moderate to severe vasculitic manifestations may be treated with short-term glucocorticoid regimens to control inflammation rapidly. They could be useful to control severe disease quickly and may help to alter the disease course if employed judiciously in a short term period or as a bridge to anti-viral agents[63]. Regimens of methylprednisolone (0.5-1.0 g/day) for three days followed by prednisone (not exceeding 1 mg/kg/day) may be appropriate in the setting of skin ulceration, sensorimotor neuropathy, glomerulonephritis, and other severe vasculitic manifestations. In the current DAA era, the role of immunosuppressive agents (often used in a maintenance therapy regimen) may be marginal. The specific role of plasma exchange and rituximab are discussed in posterior recommendations. Immunosuppression requires close monitoring of blood counts and other parameters; patients treated with glucocorticoids and cyclophosphamide should also receive prophylaxis for Pneumocystis pneumonia and surveillance for other opportunistic infections. For aggressive B-cell lymphomas (DLBCL), the therapy remains based on immunochemotherapy with anthracycline-containing regimens in combination with rituximab as in HCV-negative patients[56].

LEVEL OF EVIDENCE: 3
LEVEL OF AGREEMENT: 9.43
STRENGTH OF RECOMMENDATION: C

Recommendation C2. Plasma exchange may be added to other therapies, especially in patients with severe/life-threatening cryoglobulinemic vasculitis

Plasma exchanges remove circulating cryoglobulins from the circulation, thereby interrupting the immune complex-mediated pathogenesis of cryoglobulinaemic vasculitis. Such intervention is useful in patients with immediately life-threatening involvements[88] and for those with hyperviscosity syndrome. However, apheresis techniques do not alter the underlying disease milieu and can lead to a rebound phenomenon in which cryoglobulin production increases after the cessation of apheresis[89]. Therefore, it should always be used as complementary therapy in combination with other strategies (antiviral therapies, B-cell depleting agents). The level of evidence is based on observational clinical experience in CV[90–92].

LEVEL OF EVIDENCE: 3
LEVEL OF AGREEMENT: 9.42/10
STRENGTH OF RECOMMENDATION: C

Recommendation C3. B-cell depleting agents may currently be considered the best biological target option for patients with EHM, always with a reasonable individualized assessment of the benefits and risks.

The most promising non-antiviral therapeutic approach to HCV-related cryoglobulinaemia is rituximab (**Table 4**), although it is not licensed for EHMs and CV and should be used off-label. The level of evidence is the highest of all current therapeutic options for EHMs, both in the number of treated patients (more than 400 patients, including isolated case reports) and in the data quality (the only RCTs carried out in patients with EHMs tested rituximab). Prospective studies found better results for a combination of rituximab and the old standard antiviral therapy compared with antiviral therapy alone[45,46]. Petrarca et al[41] found excellent tolerance in cirrhotic patients, even with improvement in liver cirrhosis markers. With respect to RCTs, Sneller et al[47] conducted a randomized controlled trial comparing rituximab (375 mg/m^2/week for 4 consecutive weeks) with placebo in 24 patients refractory to antiviral therapy; after 6 months, 10 patients in the rituximab group and 1 in the control group were in remission (83% vs. 8%), a result that met the criterion for halting the trial. De Vita et al[48] reported the results of a large controlled trial including 59 refractory patients with severe HCV-related CV (skin ulcers, active glomerulonephritis, or refractory peripheral neuropathy) randomized to rituximab (two infusions of 1g fortnightly) or conventional immunosuppressive treatment (glucocorticoids, azathioprine/cyclophosphamide, or plasmapheresis). The primary end point was the proportion of patients who continued taking the initial therapy; the percentages were 71% vs. 3% at 6 months, and 61% vs. 3% at 2 years, respectively. In the two trials, no significant adverse effects of rituximab, including raised HCV-RNA viraemia or liver transaminase levels, were reported. One note of caution with regard to the use of rituximab is

the potential for the formation of immune complexes between rituximab (a chimeric monoclonal antibody) and cryoglobulinemic IgM with rheumatoid factor activity that could exacerbate the vasculitis[93].

LEVEL OF EVIDENCE: 2
LEVEL OF AGREEMENT: 9.19/10
STRENGTH OF RECOMMENDATION: B

Statement C4. The use of antiviral therapies in combination with immunosuppressant/biological agents should normally be made:

- ***Sequentially (first, use immunosuppressant/biological agents and, once the major end-organ effects have been controlled, use antiviral therapy) (option voted for by 36.4%)***
- ***Concomitantly (option voted for by 36.4%)***
- ***Case-by-case (option voted for by 27.3%)***

No clear consensus was achieved on how to combine the different antiviral and non-antiviral options and, given the lack of scientific evidence, it seems reasonable to carry out the combination on a case-by-case basis, which weighing up some specific aspects (**Box 3**).

Recommendation C5. The efficacy of therapies in EHM patients should be evaluated not only according to the virological response, but also according to the full impact of the other clinical and immunological responses achieved.

There are no internationally-agreed scores that measure therapeutic efficacy in EHMs. Until now, reported studies mainly evaluated the response in three areas: clinical, immunological and virological (**Supplementary Table 5**). Once again, the available evidence comes largely from CV studies. There is a long list of cases in which the response in the three areas is discordant, making the evaluation of the response in patients with EHMs a much more complex issue than in non-EHM HCV patients.

In the IFN era, a poor virological response was often accepted when there was an acceptable clinical response of the EHM. In the DAA era, this problem will disappear, but there may be an opposing problem: the persistence, development or worsening of EHMs in spite of clearance if the circulating viral load. The requirement for longer follow-up periods searching for late clinical responses may be recommended for some specific organs (renal or neurological involvements).

LEVEL OF EVIDENCE: 3
LEVEL OF AGREEMENT: 9.52/10

STRENGTH OF RECOMMENDATION: C

5. CONCLUSIONS

Eradication of the virus is, undoubtedly, a key target in the therapeutic approach to HCV-related extrahepatic features[62]. However, the scenario has suffered a disruptive change with the appearance of DAA, which have emerged as game-changers in HCV therapy; therefore, it may be anticipated that the therapeutic approach to HCV patients presenting with EHMs will also change dramatically.

The impact of EHMs in HCV patients in terms of prognosis, quality of life and economic costs is undeniable[94]. We recently created the International Study Group of Extrahepatic Manifestations related to HCV (ISG-EHCV), a multidisciplinary international network, with the aim of providing a homogeneous diagnostic and therapeutic approach to HCV-infected patients presenting with EHM[95]. One of the first goals of the group has been the development of the first international guidelines for the therapeutic management of these patients, as we believe that a consensus is completely necessary in the new era of DAAs, given their potential to cure the virus. Unfortunately, the current clinical experience about the use of the new DAAs in extrahepatic disease is limited (170 cases reported in the last 2 years from uncontrolled studies, principally in CV patients and some isolated cases of B-cell lymphoma, while there is no evidence on their use in other EHMs). The central role played until now by IFN is not currently supported due to the demonstrated efficacy and safety of approved DAAs, and IFN will probably disappear due to the many antiviral agents under development, with efficacy reaching nearly 100% in some cases[96]. No solid consensus was reached on the role of the glucocorticoids and immunosuppressive agents that were the former counterpart of the non-antiviral approach to EHMs (similar to IFN in regard to antiviral therapies). This lack of consensus was probably mainly related to the anticipated progressive substitution of these agents by DAA-based regimens for mild/moderate EHMs, and by rituximab (combined with plasma exchange in some cases) for severe/life-threatening involvements[97], reflecting the prospect of a glucocorticoid-free scenario in HCV patients with EHMs.

As RCTs in patients with EHMs will be extremely difficult to carry out, it may be anticipated that the level of evidence in this field will remain limited, and therefore one of the tasks that the group is currently undertaking is the worldwide collection and analysis of real-life therapeutic data on the use of the new DAAs in HCV-infected patients with EHMs, including enlisting support from the international scientific societies of the main specialties involved in the care of these patients (rheumatology, internal medicine, hepatology and haematology). In spite of the limited scientific evidence available, we are convinced that drawing up this first

consensus on EHMs will have significant benefits for the care of HCV patients presenting with such complex and potentially life-threatening manifestations, especially if the potential limit to access to DAAs due to economic issues, which may preclude universal access to these drugs, is taken into account[98]. The current document is intended to have a short shelf-life and to be rapidly revised, with more international members being added in the near future: in fact, during discussions about the current document, a significant number of questions have arisen that must be answered by future versions (**Supplementary Table 6**). In addition, the use of the new DAAs for EHMs began only two years ago, and that current clinical experience is based on only 170 cases included in uncontrolled studies with evidence being available overwhelmingly for HCV-related vasculitis, while there is no solid evidence on their use in other EHMs. The two main reasons that may advise a new revision could be the appearance of evidence based on controlled trials (difficult to predict when it could appear) and the significant increase in the number of cases treated. Taking into account that nearly 200 cases have been published in a 2-year period, it could be reasonable to think that we could have 200 additional reported cases during the next two years, making reasonable a re-evaluation of the scientific evidence at that time. Although the hoped-for definitive cure for the extrahepatic manifestations of HCV infection seems to be closer than ever, the complexity of these patients, in whom different etiopathogenic scenarios coexist, signals a more difficult therapeutic scenario than that now reported for the standard population infected with HCV.

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APPENDIX 1. Members of The Multidisciplinary International Working Group of the ISG-EHCV

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BOX 1. Organ-by-organ manifestations of HCV patients presenting with extrahepatic manifestations classified according to severity.

a) Mild/moderate manifestations
- Purpura
- Single, sporadic skin ulcers
- Arthralgia/arthritis
- Non-inflammatory musculoskeletal pain
- General features (malaise, fever)
- Mild/moderate neuropathies (sensory)

b) Severe manifestations
- Recurrent, multiple, non-healing cutaneous ulcers
- Digital ischemia
- Severe neuropathy (motor or sensory-motor)
- Glomerulonephritis with/without renal failure/nephrotic syndrome
- Interstitial lung disease
- Vasculitic gastrointestinal involvement (non-necrotizing)
- Severe autoimmune cytopenias (symptomatic haemolytic anaemia/thrombocytopenia)

c) Life-threatening manifestations
- Rapidly progressive glomerulonephritis
- CNS involvement
- Acute intestinal necrotizing vasculitis
- Alveolar haemorrhage
- Coronary artery involvement (excluding other etiologies)

BOX 2. Evaluation Prior to Starting Therapy of HCV-related EHM

- Full medical history and clinical examination
- Full blood count
- Liver biochemistry, glycaemia, HbA1C, lipid profile
- Renal function tests (creatininemia, urinalysis, proteinuria)
- Autoantibodies (ANA, RF)
- Cryoglobulin: search and, if positive, immuno-typing and quantitative dosage
- C3 and C4 complement levels
- Serum protein immunofixation
- Noninvasive assessment of stage of liver fibrosis
- Abdominal ultrasoun
- Chest X-ray
- HCV genotyping
- Quantitative HCV-RNA by sensitive assay (low limit of detection 25 IU/ml)
- Measurement of EHM disease activity (FFS or BVAS for vasculitis, SLEDAI for lupus, ESSDAI for Sjögren…)

BOX 3. Pros and Cons listed by ISG-EHCV members regarding the concomitant or sequential use of antiviral and non-antiviral therapies.

	Concomitant use	Sequential use
PROS	Rapid complete response obtained with the concomitant use of RTX and DAA No safety issues in using them concomitantly when required Start the two treatments as soon as possible concomitantly due to the non-immediate response to some non-antiviral options (i.e., RTX), since they do not interfere each other. Benefits of the simultaneous viral load clearance and autoimmune damage produced by HCV The concomitant administration of glucocorticoids/immunosuppressive agents along with antiviral therapy would help stop the inflammatory/autoimmune response triggered by the virus and, at the same time, eliminate the circulatory virus. This approach is used in similar situations, for example, hemophagocytic syndrome, were both anti-inflammatory drugs (including biologicals) are given along with antiviral therapy in the case of a virus-associated-hemophagocytic syndrome.	Easier to differentiate the potential side effects related to the different therapeutic options B lymphocyte depletion induced by rituximab can facilitate the therapeutic activity of antiviral drugs, administered later. Probably, sequential regimens will be better tolerated than the concomitant ones. In patients with severe EHMs, the use of antiviral therapies in combination with immunosuppressant/biological agents should be sequentially, carefully adjusted in patients with renal failure until there is more data showing they are safe in severe/life-threatening situations.
CONS	HCV treatment monitoring could be difficult in patients with renal failure, so renal function should be stabilized first before HCV treatment is initiated. Severe renal, pulmonary or neurologic affection may make antiviral therapy difficult In IFN-based regimens, IFN may exacerbate the cryoglobulinemic vasculitis if not properly controlled before treatment. Potential risk of enhanced toxicity (i.e., haematological} associated with their concomitant use. The priority should be given to immunosuppression especially in severe or life threatening diseases. Uncertainty about potential side effects of DAAs in cryoglobulinemic patients with high cryocrit levels (autoimmune-induced features by immune complexes?)	Hepatic damage may be exacerbated by the use of glucocorticoids/immunosuppressive /biologic agents in the absence of concomitant antiviral therapy The abrupt removal of immunosuppressive therapies may induce symptoms rebound needing to suspend the etiologic treatment and/or be misinterpreted as intolerance/side effects or no clinical response

Table 1. Clinical, immunological and virological responses in HCV patients with EHMs treated with DAA-based regiments[23–54]

	Antiviral agent famílies		Clinical response			Immunological response			Virological response	
Patients (n)	**IFN/RBV**	**DAAs**	**CR**	**PR**	**NR**	**Cryoglob. clearance**	**C4 levels improv**	**RF reduction**	**SVR**	**Evaluation (weeks)**
41	pIFN+RBV	BCP/TLP	29/39	9/39	1/39	14/28	nd	nd	26	12-72
9	pIFN+RBV	SOF (5), SIM+SOF (2), ASP+DCV (2)	6/7	0/7	1/7	6/7	4/5	4/5	8	24-83
50	**pINF-RBV**	**BCT/TLP (41), SIM (2), ASP (2), DCV (2), SOF (7)**	**35/46 (76%)**	**9/46 (20%)**	**2 de 46 (4%)**	**20/36 (56%)**	**4/5 (80%)**	**4/5 (80%)**	**34 (68%)**	**12-83w**
48	RBV	SOF	23/30	4/30	3/30	13/29	2/3	1/3	40/47	12-36
6	RBV	SIM+SOF	nd	nd	nd	nd	nd	nd	6	24
5	RBV	LDV+SOF (3), PTP+OMT+DSB+RTN (1), DCV+SOF (1)	0/1	1/1	0/1	1/1	nd	nd	5	24
59	**RBV**	**SOF (58), PTP (1), OMT (1), DSN (1), RTN (1), SIM (6), DCV (1), LDV (3), RTN (1)**	**23/31 (74%)**	**5/31 (16%)**	**3/31 (10%)**	**14/30 (47%)**	**2/3 (67%)**	**1/3 (33%)**	**51/58 (88%)**	**12-36w**
25	Free	DCV/LDV+SOF	11/15	3/15	1/15	5/14	9/12	7/8	24	4-12
18	Free	SIM+SOF	5/11	4/11	2/11	7/10	5/7	1/3	17	12-24
12	Free	PTP+OMT+DSB+RTN	10	0	2	5	5/12	6/7	12	12-24
6	Free	SIM+DCV (3), GZR+EBR (2), FDP+DLB (1)	2	1	3	3	4	3/4	6	24
61	**Free**	**DCV/LDV (28), SOF (43), SIM (21), PTP (12), OMT (12), DSB (12), RTN (12), GZB(2), EBR (2), FDB (1), DLB (1)**	**28/44 (64%)**	**8/44 (18%)**	**8/44 (18%)**	**20/42 (48%)**	**23/36 (64%)**	**17/23 (74%)**	**59 (97%)**	**4-24w**

pIFN: pegylated interferon alpha; RBV: ribavirin; DAAs: direct-acting agents; BCP: boceprevir; TLP: telaprevir; PTP: paritaprevir; SIM: simeprevir; OMT: ombitasvir; DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; DSB: dasabuvir; RTN: ritonavir ; ASP: asunaprevir; GZR: grazoprevir; EBR: elbasvir; FDP: faldaprevir; DLB: deleobuvir; CR: complete response; PR: partial response; NR: non response; nd: : not detailed; C4:complement 4; RF: rheumatoid factor; SVR: sustained virologic response.

Table 2. Use of IFN-containing DAA therapeutic regimens in patients with HCV-related CV (studies including 3 or more patients; case reports including 1 or 2 patients are summarized in the Supplementary Table 7)

Author (year)	Design	N	Age/gender Genotype	Patient profil·le	Previous therapies (*ongoing*)	Cryo type	IFN-containing regimen	DAA (duration)	Clinical response (evaluation)	Immunological response	Virological response (SVR, follow-up)
Gragnani et al (2014)	Retrospective	5	62 yrs, 3W 1Ia, 4Ib	Systemic CV (all neuropathy)	ND	ND	pIFN+RBV	BCP (5) (48w)	CR = 5 (100%) Relapses after stop antiviral tx = 5	ND	SVR = 0 (0%) * (24w)
Cornella, Stine (2015)	Case series	3 3	49 yrs, 2W 2I, 1Ia 51,3 yrs, 2W 2I, 1ND	Severe, refractory CV Refractory CV	RTX (1) RTX (3) Cs (1) Telaprevir (breaktrough at 4w)	ND ND	pIFN+RBV pIFN+RBV	BCP (1) TLP (2) SOF (3, one + RTX)	NR (RTX-refractory neropathy) PR (severe neurop) CR (late CR in GN) Neuropathy NR Not evaluable (GN already responded) Not reported (RTX increased viral load)	Cryo clearance = 0/3 Cryo clearance = 2/3	SVR = 3 (72 w) SVR = 3 (100%) (72 w)
Saadoun et al (2015)	Prospective	30	59 yrs, 17W 10Ia,20Ib	Severe/refractory CV	RTX (13, ***ongoing 7***) ***Cs (6)*** pIFN-RBV (23)	II (26) III (4)	pIFN+RBV	BCP (13) TLP (17) (72w)	CR = 22 (67%) PR = 8 (23%) Relapses = 2 Mean BVAS reduction (p<0.001)	Cryo clearance = 13/24 (56%) Reduction serum cryo (<0.001) Improvement C4 levels (0.02) Reduction serum RF (>0.05)	SVR = 20 (67%)** (72w)
Bonacci et al (2016)	Prospective	5	ND	CV	ND	ND	pIFN+RBV	SIM+SOF (2) SOF (1) ASP+DCV (2)	CR (5)	Cryo clearance = 4 Improv. C4 levels = 4 Reduction RF = 4	SVR = 4 (24w)

**3 virological breakthrough, 2 withdrawal due to hematological side effects; **Ongoing RTX: 4SVR, 3 no response; ongoing cortis: 3SVR, 3 no response*

N: number; w: week; yrs: years; PN: polyneuropathy; HIV: human immunodeficiency virus; CV: cryoglobulinemic vasculitis; Cs: corticosteroids; PEx: plasma Exchange; MMF: mycophenolate mofetil; RTX: rituximab; pIFN: pegylated interferon alpha; RBV: ribavirin; Cryo: cryoglobulins; DAA: direct-acting antiviral; BCP: boceprevir; TLP: telaprevir; CR: complete response; PR: partial response; NR: non response; ND: not detailed; GN: glomerulonephritis; BVAS: Birmingham Vasculitis Activity Score; RF: rheumatoid factor; SVR: sustained virologic response. N: number; w: week; yrs: years; IPT: idiopathic purpura thrombocytopenic; CV:cryoglobulinemic vasculitis; Cs: corticosteroids; IVIG: intravenous immunoglobulin; aza: azathioprine; RTX: rituximab; pIFN: pegylated interferon alpha; RBV: ribavirin; Cryo: cryoglobulins; DAA: direct-acting antiviral; SOF: sofosbuvir; CR: complete response; NR: non response; ND: not detailed; GN: glomerulonephritis; SVR: sustained virologic response.

Table 3. Use of IFN-free DAA therapeutic regimens in patients with EHMs (studies including 3 or more patients; case reports including 1 or 2 patients are summarized in the Supplementary Table 7)

3a. Ribavirin-containing regimens

Author (year)	Design	N	Age/gender Genotype	Patient profile	Previous therapies (*ongoing*)	Cryo type	Drugs	Clinical response (evaluation)	Immunological response	Virological response (follow-up)
Sise et al (2015)	Retrospective	4	ND	Active CV	***RTX (3)*** ***Cs (1)***	II (4)	RBV SOF	CR = 1 PR = 1 NR = 2	Cryo clearance 1/3 Cryo reduction 1/3 Raised C4 2/3 RF reduction 1/3	SVR12 = 3
Saadoun et al (2015)	Prospective	24	56 yrs, 11W 6Ia, 6Ib	Active CV	RTX (4, ***ongoing 3***) Cs (4, ***ongoing 2***) PEx (2)	II (19)	RVB SOF	CR = 21 (87.5%) PR = 3 (12.5%)	Cryo clearance 11 (46%) Reduction serum cryo (<0.05) Improvement C4 levels (<0.05)	SVR24 = 17/23 (74%)
Gragnani et al (2016)	Prospective	28	x = 63,5 16W,12M 1Ia,7Ib,13II,4III,3IV	CV Cirrhosis = 12	IFN = 18	Nd	RBV SOF (18) SOF+SIM (6) SOF+LED (3) SOF+DCV (1)	ND	ND	SVR24=28

N: number; w: week; mo: months; M: man; W: woman; mg: milligram; d: day; MZL: marginal zone lymphoma; SMZL: splenic marginal zone lymphoma; CV: cryoglobulinemic vasculitis; Cs: corticosteroids; PEx: plasma Exchange; RTX: rituximab; IFN: interferon alpha; RBV: ribavirin; Cryo: cryoglobulins; DCV: daclatasvir; SOF: sofosbuvir; OMT: ombitasvir; PTP: paritaprevir; RTN: ritonavir: DSB: dasabuvir; SIM: simeprevir; CR: complete response; PR: partial response; NR: non response; ND: not detailed; RF: rheumatoid factor; C4: complement 4; SVR: sustained virologic response. 3T (OMT,PTP,RTN,DSB)

3b. Ribavirin-free regimens

Author (year)	Design	N	Age/gender Genotype I	Patient profil·le	Previous therapies (*ongoing*)	Cryo type	Drugs	Clinical response (evaluation)	Immunological response	Virological response (SVR12)
Sise et al (2015)	Retrospective	8	ND	Active CV	Cs (2) PEx (1) CYC (1) RTX (1) ***USTK (1)***	ND	SOF + SIM	CR = 4 PR = 4	Cryo negativ 4/6, reduction 2/6 Raised C4 4/6 RF reduction 0/2	SVR12 = 7/8
Sollima et al (2016)	Case series	5	72,5, 2W Ib,Ib 65, 2M Ia, II 46M IV	Refractory CV	RTX and/or IFN-RBV	Nd Nd Nd	3T SOF + DCV SOF + SIM	NR = 2 CR = 1, NR = 1 NR	Cryo negativ 1/2 Cryo negativ 1/2 Cryo negativ 1	SVR12 = 2/2 SVR12 = 2/2 SVR12
Bonacci et al (2016)	Prospective	30	ND	CV	Nd	Nd	3T (10) LDV+SOF (10) SIM+DCV (3) GZR+EBR (2) SIM+SOF (2) DCV+SOF (2) FDP+DLB (1)	CR (10) CR (8), PR (2) CR (1), PR (1), NR (1) CR (1), NR (1) CR (1), NR (1) CR (1), PR (1) NR (1)	Cryo negativization (12) Improv. C4 levels (19) RF reduction (17/21)	SVR24 = 29
Gragnani et al (2016)	Prospective	16	x = 64,37 12W,4M 1Ia,14b,1III	CV Cirrhosis = 5	IFN = 7	Nd	LDV+SOF (7) SIM+SOF (6) DCV+SOF (3)	Nd	Nd	SVR24 = 16

N: number; w: week; M: man; W: woman; CV: cryoglobulinemic vasculitis; Cs: corticosteroids; PEx: plasma Exchange; CYC: cyclophosphamide; RTX: rituximab; USTK: ustekinumab; IFN: interferon alpha; RBV: ribavirin; Cryo: cryoglobulins; 3D: ombitasvir/paritaprevir/ritonavir and dasabuvir; DCV: daclatasvir; LDV: ledipasvir; SOF: sofosbuvir; SIM: simeprevir; CR: complete response; PR: partial response; NR: non response; ND: not detailed; RF: rheumatoid factor; SVR: sustained virologic response.

Table 4. Use of rituximab in patients with HCV-related cryoglobulinemic vasculitis

Author (year)	Patient profile	Study design (follow-up)	Therapeutic intervention (number of patients)	Control group	Therapeutic response (study group vs control group)	Adverse events
Zaja et al, (2003)	Refractory	Prospective (24w)	RTX 375 mg/m² x 4w (n= 15)	No	- CR: purpura 11/12, cutaneous ulcers 5/5, neuropathy 7/7, glomerulonephritis 1/2, B-cell lymphoma 3/3 - IR: reduced RF, cryoglobulins, IgM levels; increased C4 levels	Total AE: 13% Discontinuation: 6.6% Death: 0% Relapses: 33%
Sansonno et al, (2003)	Refractory to IFN	Prospective	RTX 375 mg/m² x4w (n=20)	No	- CR: complete 80%	Total AE: no severe effects Discontinuation: 0% Death: 0% Relapses: 25%
Petrarca et al, (2010)	Cirrhosis	Prospective (24w)	RXT 375 mg/m² x4w (n= 19)	No	- CR: complete in 12/19, partial 7/19. - Improvement ascitis	No severe side effects
Ferri et al, (2011)	Refractory/lack of tolerance to IFN	Retrospective + Pubmed search (24w)	RXT 375 mg/m² x 4w (n=87)	No	- CR: purpura (74%), cutaneous ulcers (87%), neuropathy (44%).	Total AE: 7 % Discontinuation: 4.5 % Death: 0% Relapses: NA
Visentini et al, (2011)	Refractory/lack of tolerance to IFN	Prospective	RTX 250 mg/m² x 2w (n= 27)	No	- CR: 79% - Mean time of relapse: 6,5m	Total AE: 11.1% Discontinuation: 3.7 % Death: 11.1 % (unrelated to RTX) Relapses: 42 %
Saadoun et al, (2008)	Refractory/relapse	Prospective (48w)	IFN-α-Peg 2b + RBV + RTX 375 mg/m² x 4w (n= 16)	No	- CR: Clinical improvement 94%; complete response 62% - VR: in all patients with complete clinical response - IR: decreased cryoglobulin (p=0.01) and RF (p=0.01), increased C4 (p=0.009) levels.	Total AE: 75% Discontinuation: 12.5% Death: 6.25% Relapses: 12.5%
Terrier et al, (2009)	Refractory/relapse	Case-control (48w)	IFN-α-Peg/RBV x 48w + RTX 375 mg/m² x 4w (n=20)	RTX 375 mg/m² x 4w (n=12)	- CR: complete (80% vs. 58%), partial (15% vs. 9%) - IR: complete (67% vs. 46%), partial (33% vs. 36%) - VR: 55% vs. 0%	Total AE: 25% vs 25% Discontinuation: 25% vs 0 % Death: 0% vs 0% Relapses: 15% vs 33%
Dammacco et al, (2010)	Naïve	Case-control (48w)	IFN-α-Peg/RBV x 48w + RTX 375 mg/m² x 4w (+ 2 additional infusions at 5m and 10m) (n=22)	IFN-α-Peg/RBV x48w (n=15)	- CR: complete (54.5% vs 33.3 %) (p<0.05). - VR: 83% vs 40 % (p= <0.01).	Total AE: 22.7% vs 53% Discontinuation: 0% vs 0% Death: 0% vs 0% Relapses: 16.6% vs 60%
Saadoun et al, (2010)	Naïve	Case-control (48w)	IFN-α-Peg/RBV x 48w + RTX 375 mg/m² x 4w	IFN-α-Peg/RBV x48w (n=55)	- Time to clinical remission (5.4±4 vs 8.4±4.7m, p=0.004) - Renal response (80.9% vs 40% CR,	Total AE: 55.3% vs 54.5% Discontinuation: 13.2 % vs 9.1%

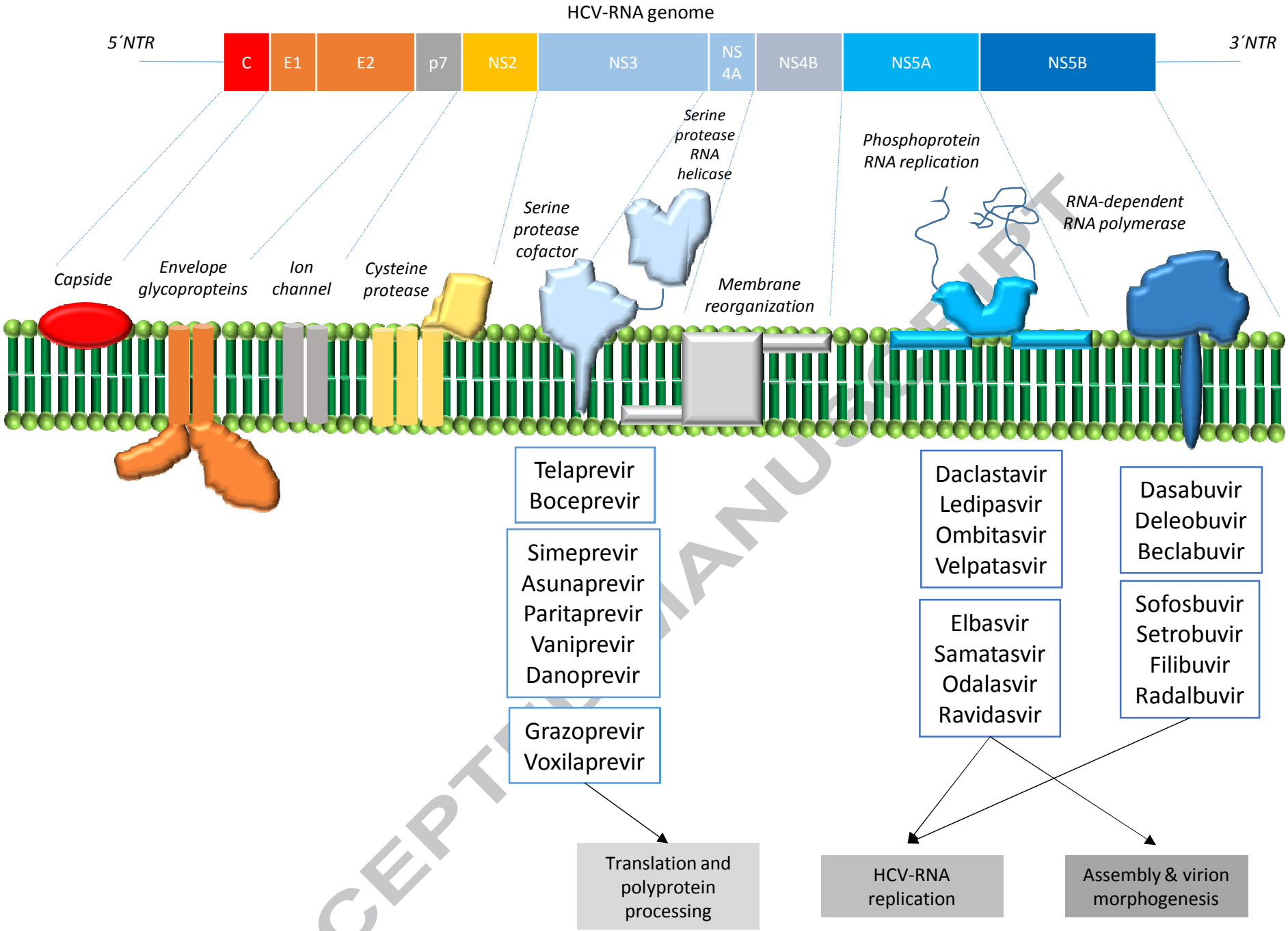
			(n=38)		p=0.040) - Cryoglobulin negativization (68.4% vs 43.6%, p=0.001).	Death: 0% vs 0% Relapses: 18.4% vs 54.5%
Sneller et al, (2012)	Refractory/lack of tolerance to IFN	RCT	RTX 375 mg/m2/s x 4w (n=12)	Standard of care with immunosuppressive agents (n=12)	- CR at 6m: 83% vs 8% ($P < 0.001$).	Total AE: 67% vs 67% Discontinuation: 8.3 % vs 0 % Death: 0% vs 0 %
De Vita et al, (2012)	Refractory/lack of tolerance to IFN	RCT (24m)	RTX 1g. x 2 fortnight (n=28)	Standard of care with immunosuppressive agents (n=29)	**Primary outcome** Survival of treatment at 12m (64.3% vs 3.5%, p<0.0001) and 24m (60.7% vs 3.5%; p<0.0001). **Secondary outcome** Birmingham Vasculitis Activity Score decreased only after treatment with RTX (11.9 at baseline to 7.1 $P < 0.001$).	Total AE: 26.1 % vs 10.3% Discontinuation: 7.1 % vs 0 % Death: 10.2% vs 3.4 % Relapses: 14.3 % vs 86.3%
Visentini et al (2015)	Refractory/relapse to IFN-RBV, or intolerance	Phase II trial single arm	Rituximab 250 mg/m2 x2 fortnight (n=52)	No	**Primary outcome** CR (BVAS = 0) or PR (BVAS reduction > 50%) = 41/48 (85%) **Secondary outcome** Cryo clearance or > 50% reduction = 26/48	Total AE = 6 (11.5%) Death = 6 (11.5%) Relapses in 17/41 responders (41%)
Quartuccio et al (2015)	Refractory/lack of tolerance to IFN	Extension study of De Vita 2012	RTX 1g. x 2 fortnight No retreated (n=13) Retreated (n=17)	No	Clinical response (available in 11 of 17 retreated) CR in 4, PR in 4, NR in 3	Total AE = 9/30 (30%) Death = 6 (20%)
Roccatello et al (2016)	Refractory/intolerant CV, severe hematological involvement	Prospective	RTX 375 mg/m2/s x 4w + 2 additional RTX infusions 1 and 2 months later (4+2 regimen) (n=31)	No	Clinical response CR = 20 (65%), PR = 10 (32%), NR = 1 (3%)	Total AE = 10 (32%) Death = 6 (19%) Relapses in 9/30 responders (30%)

n: number; w: week; m: month; mg: milligram; m2: square meter; d: day; g: gram; CV: cryoglobulinemic vasculitis; RCT: randomized controlled trial; RTX: rituximab; IFN: interferon alpha; IFN-α-Peg: pegylated interferon alpha; RBV: ribavirin; CR: complete response; IR: incomplete response; PR: partial response; NR: non response; RF: rheumatoid factor; C4: complement 4; Ig: serum immunoglobulin; VR: virologic response; vs: versus; BVAS: Birmingham Vasculitis Activity Score; Cryo: cryoglobulins; AE: adverse events; NA: not available.

Table 5. Side effects of DAA in patients with HCV-related cryoglobulinemic vasculitis: comparison between regimens with and without IFN[29,32,33]

Side effects	**IFN-associated N = 30**	**IFN-free N = 36**	**Bilateral p value**
Fatigue	20/23 (87)	7 (19)	**<0.001**
Depression	5/23 (22)	0 (0)	**0.007**
Insomnia/irritability	0 (0)	9 (25)	**0.003**
Nausea	5/23 (22)	3 (8)	0.241
Toxic skin reaction	2/23 (9)	2 (6)	0.639
Pruritus	9/23 (39)	2 (6)	**0.002**
Anaemia (Hb < 11 g/L)	17/23 (74)	8 (22)	**<0.001**
Epo use	28 (93)	13 (36)	**<0.001**
Red-cell transfusion	14 (47)	3 (8)	**0.001**
Neutropenia (<1500)	20/23 (87)	nd	nd
G-CSF use	2 (7)	0 (0)	0.203
Thrombocytopenia (<100,000)	15/23 (65)	nd	nd
Infection	11/23 (48)	6 (17)	**0.022**
Discontinuation	8 (27)	3 (8)	0.202
Death	1 (3)	2 (6)	1.000

IFN: interferon alpha; Hb: hemoglobin; G-CSF: Granulocyte-colony stimulating factor; nd: not detailed



Abstract: *The current therapeutic armamentarium against HCV has been recently expanded with an explosion of new molecules (DAAs) with high virological efficacy
*The objective of this international consensus is to provide therapeutic recommendations for HCV patients with extrahepatic manifestations (EHM).
*The use of non-antiviral therapeutic approaches should be evaluated according to the type of EHM and severity of the clinical presentation
*B cell depletion with rituximab is the established biologic approach to cryoglobulinaemic vasculitis (CV) employed to date.
*The efficacy of therapies in EHM patients should be evaluated not only according to the virological response, but also according to the full impact of the other clinical and immunological responses achieved.
*Clinical experience of the use of the new DAAs in EHM remains very limited, with less than 100 cases reported in the last 2 years (overwhelmingly in CV patients)

Keywords: Hepatitis C Virus; extrahepatic manifestations; DAAs; rituximab