Therapeutic management of extrahepatic manifestations in patients with chronic hepatitis C virus infection

M. Ramos-Casals, O. Trejo, M. García-Carrasco and J. Font

The hepatitis C virus (HCV) is a linear, single-stranded RNA virus of the Flaviviridae family that was identified in 1989 and is recognized as the major causal agent of non-A, non-B hepatitis [1]. HCV infection is emerging as an extremely common and insidiously progressive liver disease that is often associated with extrahepatic manifestations, including autoimmune disorders. The clinical relevance of these phenomena is extremely variable, ranging from subclinical features or laboratory abnormalities to overt clinical manifestations that may be severe in some patients.

A decade ago, various authors described the association of chronic HCV infection with a heterogeneous group of non-hepatic conditions, such as pulmonary fibrosis, cutaneous vasculitis, glomerulonephritis, Mooren’s ulcer, porphyria cutanea tarda and lichen planus [2], which were regarded as extrahepatic manifestations of chronic HCV infection, though weak association has been found in some of these conditions. Moreover, there has been a growing interest in the relationship between chronic HCV infection and systemic autoimmune diseases, mainly Sjögren’s syndrome, rheumatoid arthritis (RA), polyarteritis nodosa (PAN), antiphospholipid syndrome and systemic lupus erythematosus, although most of the data are based on small series and case reports. In addition, the predominant role of cryoglobulinaemia in the autoimmune features associated with chronic HCV infection has been increasingly accepted [3].

Diagnosis and treatment of HCV-related autoimmune features has become a clinical challenge in HCV-infected patients, in whom chronic liver disease associated with severe autoimmune features may contribute to a very poor prognosis. Although the primary goal in the treatment of patients with chronic HCV infection is the eradication of the virus with combined antiviral therapy, there are few data on the efficiency and safety of this therapy in patients with chronic HCV infection with autoimmune features, as the majority of patients on immunosuppressive regimens or with autoimmune/extrahepatic conditions were excluded from the multicentre trials [4]. The treatment guidelines for HCV-associated extrahepatic features should be based not only on the pathogenic mechanisms, but also on the accurate, individual assessment of the activity/severity of both extrahepatic clinical features and the underlying liver disease [5].

Therapeutic options

Adequate management of HCV-related extrahepatic features should be targeted at two independent (although closely related) goals. The first is the eradication, or at least the reduction, of the circulating viral load with conventional HCV antiviral therapy. The second is the treatment of autoimmune features using corticosteroids, cytotoxic agents and/or plasmapheresis, in order to control the formation, tissue deposition and inflammatory effects of immune complexes.

Antiviral therapy

The drug regimens available for treating chronic HCV infection are monotherapy with interferon α (IFN-α) and combined therapy with IFN-α and ribavirin [4]. Their use in patients with HCV-related autoimmune features is controversial due to the lack of available data, as these patients were excluded from multicentre trials due to a potential lack of response to treatment and the appearance of severe side-effects and/or drug toxicity [6]. However, recent case reports and small series suggest that the use of antiviral therapies in patients with chronic HCV infection and autoimmune manifestations may be efficient and safe.

Interferon α. IFN-α treatment is recommended in patients with autoimmune features and proven evidence of replicative HCV infection. IFN-α had been proved to be effective in some patients with mixed cryoglobulinaemia (MC) before the identification of HCV and its association with MC [7, 8]. In the 1990s, several groups [9–13] reported the benefits of IFN-α in HCV-associated cryoglobulinaemia, although these benefits are limited to patients in whom HCV RNA disappears from serum. This supports other studies in
which the clinical and biochemical response to IFN-α is associated with loss of HCV RNA from serum and long-term remission of the chronic liver disease is associated with the sustained absence of viraemia [14]. Meticulous monitoring during IFN-α therapy is needed because, on the one hand, flares of aminotransferases without subsequent HCV RNA clearance have been observed [15, 16] and, on the other hand, IFN-α therapy is associated with numerous side-effects, which lead certain patients to discontinue the therapy [17, 18]. Side-effects occurring during the first 2 weeks of administration include fever, chills, myalgias, anorexia and an influenza-like syndrome. Long-term side-effects include cytopenias, precipitation of autoantibodies, alopecia, lupus-like autoimmune disease, vasculitis, severe psychological disturbances and increased bacterial infection. The new long-acting peglated IFN-α preparation should result in improved tolerability, and recent studies in patients with chronic HCV infection have been completed with good results [19–21].

Ribavirin. Ribavirin monotherapy may be effective in IFN-α-intolerant patients with symptomatic HCV cryoglobulinaemia, although its use in patients with renal involvement should be monitored carefully and the effect is not sustained when therapy is discontinued [22]. Misiani et al. [23] found that reduced-dose ribavirin therapy may produce severe side-effects in some patients, such as anaemia requiring blood transfusions and erythropoetin therapy, and widespread pruriginous rash resulting in discontinuation of therapy. Zuckerman et al. [24], using an initial dose of 600 mg daily in patients with severe renal failure, described discontinuation of therapy in one patient (due to severe reduction of haemoglobin levels) and a mild reduction in haemoglobin concentration in three others (<2 g/day).

Corticosteroid and immunosuppressive therapies

Little has been published on the outcome of corticosteroid therapy in patients with chronic HCV infection. The poor disease course of patients with hepatitis B virus treated with corticosteroids [25] led to the suggestion hypothesis that HCV viraemia would be increased in patients treated with these drugs. Some studies have described a rapid progression of liver disease in immunosuppressed patients with chronic HCV infection, i.e. patients coinfected with HIV and HCV and transplanted patients [26, 27]. Other studies found that corticosteroids increased HCV viraemia when given for a short time (1–6 months) and that when corticosteroids were withdrawn the viraemia reverted to previous levels [28, 29].

However, the use of corticosteroids in patients with chronic HCV infection with autoimmune features has been reconsidered recently. Thiele et al. [30] found a favourable response to corticosteroid therapy in patients with chronic HCV infection. Another study showed neither an apparent increase in HCV RNA nor worsened liver function when steroids were combined with IFN-α to treat HCV-associated MC [8]. A favourable response of combined autoimmune HCV hepatitis to prednisone alone or in combination with azathioprine [31] has also been reported. Nevertheless, caution is warranted because the long-term effects of corticosteroids on the liver function of patients with chronic HCV infection remain unknown [6].

Therapy with immunosuppressive agents in patients with HCV-related autoimmune features has been little studied. Cyclophosphamide [32], azathioprine [33], plasmapheresis [34] and intravenous immunoglobulins [35] have been used in some patients with chronic HCV infection, although their effects on liver function have not been evaluated and immunoglobulins may also contain anti-HCV antibodies [36]. We found higher rates of morbidity and mortality in patients with chronic HCV infection receiving immunosuppressive therapies, possibly related to the severity of coexisting hepatic and autoimmune manifestations.

Management of autoimmune features

Few treatment-related data are available on the management of the numerous extrahepatic manifestations and autoimmune disorders associated with chronic HCV infection. Recent studies have demonstrated that antiviral therapy, as well as corticosteroids and immunosuppressive therapies, may be effective in managing extrahepatic HCV manifestations, although discontinuation often produces relapses [30, 37–39]. However, the potential improvement of symptoms and reduction of viraemia must be balanced against the adverse effects of medication, which include IFN-α-induced autoimmune phenomena, ribavirin toxicity and possible exacerbation of HCV infection caused by immunosuppressive agents [40].

Arthritic involvement

Arthralgias. Arthralgias are common in patients with chronic HCV infection: Cacoub et al. [41] reported a prevalence of 19% in a large series of HCV patients. In our opinion, the management of arthralgias in patients with chronic HCV infection should be non-aggressive, consisting of resting and analgesia with paracetamol 1–4 g/day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) requires individual evaluation as they are contraindicated in patients with cirrhosis, although Buskila et al. [33] reported a good response to NSAIDs in eight patients with chronic HCV infection and arthralgias. In selected cases we have used the new anti-cyclooxygenase 2 (anti-COX-2) drugs with a good clinical response and no worsening of liver function.

Arthritis. Overt arthritis occurs less frequently than arthralgias, with a prevalence of less than 5% in the main series of patients with chronic HCV infection, and it is usually related to an associated cryoglobulinaemic syndrome. The pattern of arthritis in these patients is intermittent, mono- or oligoarticular and non-erosive, affecting large and medium-sized joints. Several studies have analysed the therapeutic management of HCV-related arthritis in small series of patients. Buskila et al. [33] described four patients with arthritis: three responded well to NSAIDs plus low
doses of prednisone, whereas the fourth patient showed severe, persistent arthritis refractory to different NSAIDs, oral steroids and intramuscular gold injections; in this patient the addition of azathioprine resulted in a moderate improvement. Lovy et al. [42] reported a good response to hydroxychloroquine and low doses of prednisone (5 mg/day or less) in 19 patients with chronic HCV infection with rheumatic manifestations (15 fulfilling diagnostic criteria for RA), with no evidence of arthritis progression. Bon et al. [43] described four patients with chronic HCV infection with synovitis and/or arthritis who completed a 6-month course of well-tolerated IFN-α, with improvement of articular involvement.

Although the optimal treatment for HCV-related polyarthritis has not yet been determined, it seems that NSAIDs, prednisone and hydroxychloroquine can be used with success and minimal complications [42-47]. We suggest step-by-step therapeutic management for HCV-related arthritis according to its severity and response to treatment (Table 1). The first step should be rest and analgesia, followed by the use of NSAIDs with close monitoring (in non-cirrhotic patients) or anti-COX-2 therapy. The second step should be the use of antimalarial drugs (indicated in patients with a lupus-like disease) and low doses of corticosteroids (<15 mg/day). The use of immunosuppressive agents, such as methotrexate and azathioprine, should be considered for severe and refractory arthritis in individual cases, with close monitoring of liver function, HCV RNA levels and cell counts.

**Muscular involvement**

There are various reports of polymyositis (PM) associated with chronic HCV infection [48-50] and different therapeutic options have been used, with controversial results. On the one hand, corticosteroids have been indicated in some patients. Buskila et al. [33] described in one case a reduction in symptoms and enzyme levels after prednisone therapy, while Alric et al. [35] reported that corticosteroids increased serum alanine aminotransferase in two patients, leading to severe liver damage in one. Although some authors have used IFN-α monotherapy to treat HCV-related PM with the same controversial outcome: some patients responded well, others presented severe aggravation of PM after IFN-α discontinuation and several worsened, or IFN-α precipitated myositis [35, 51]. Alric et al. [35] described the improvement of PM after intravenous gammaglobulin treatment in two patients who relapsed after IFN-α discontinuation. In the light of these results, HCV-related PM should be considered an extrahepatic condition of chronic HCV infection for which therapeutic management is difficult, needing careful individual evaluation when considering the use of corticosteroids and/or IFN-α. More studies are necessary to define the best treatment for PM associated with HCV.

**Cutaneous involvement**

Numerous case reports have suggested an association between HCV and vasculitis [2, 52]. Patients with HCV-associated vasculitis may present palpable purpura, urticaria or livedo reticularis, most of which present as leucocytoclastic vasculitis associated with cryoglobulinaemia [52, 53]. The most frequent clinical situation is palpable purpura in the legs, requiring non-aggressive management consisting of changes in posture, rest and, in some cases, low doses of corticosteroids (0.1-0.5 mg/kg/day). Severe cutaneous complications, such as ulcers, necrosis and gangrene (overwhelmingly related to cryoglobulinaemic vasculitis), require intensive immunosuppressive therapy with higher doses of corticosteroids, pulses of cyclophosphamide, intravenous gammaglobulins or prostacyclins, and must be monitored closely. Other cutaneous conditions may be associated with chronic HCV infection. The treatment of HCV patients with porphyria cutanea tarda remains uncertain, although one preliminary report suggests a favourable response after phlebotomy [54]. Lichen planus, psoriasis and vitiligo may be induced or exacerbated by IFN-α therapy [55-62].

**Renal involvement**

There is epidemiological evidence of an association between chronic HCV infection and renal disease [9, 63]. HCV-associated glomerulonephritis is well documented and includes membranous, membranoproliferative and acute proliferative glomerular disease [9, 12, 64, 65] as well as that associated with cryoglobulinaemia [66, 67]. Approximately 30% of patients with chronic HCV infection and renal involvement have complete or partial remission of their renal disease; 30% suffer from intermittent exacerbations and remissions; 30% have an indolent course and end-stage renal disease may not occur for several years in spite of persistent urinary abnormalities; and 10% may develop chronic renal failure [68, 69]. In HCV-related glomerulonephritis, an important aspect must be considered before the onset of therapy with antiviral and/or immunosuppressive agents: the histological demonstration and classification of inflammatory glomerular damage in the renal biopsy, because other non-inflammatory causes of renal involvement

**Table 1. Step-by-step therapeutic management of HCV-related arthritis**

<table>
<thead>
<tr>
<th>Step</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>First step</td>
<td>Rest and paracetamol</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory drugs</td>
</tr>
<tr>
<td></td>
<td>NSAIDs (contraindicated in cirrhotic patients)</td>
</tr>
<tr>
<td></td>
<td>Anti-COX-2 agents</td>
</tr>
<tr>
<td>Second step</td>
<td>Chloroquine/hydroxychloroquine (especially in patients with lupus-like disease)</td>
</tr>
<tr>
<td></td>
<td>Low doses of prednisone (&lt;15 mg/day)</td>
</tr>
<tr>
<td>Third step</td>
<td>Antimalarial drugs plus low doses of prednisone</td>
</tr>
<tr>
<td></td>
<td>High doses of prednisone (0.5–1 mg/kg/day)*</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive agents (azathioprine, methotrexate)*</td>
</tr>
</tbody>
</table>

*Requires close monitoring of liver function, HCV RNA levels and cell counts.
(such as hepatorenal syndrome in cirrhotic patients) may exist in patients with chronic HCV infection.

**Membranoproliferative glomerulonephritis**

The current understanding of the association between chronic HCV infection, mixed cryoglobulinaemia and glomerular disease has prompted the use of antiviral agents in these patients in monotherapy or combined regimes (Table 2). The most frequent treatment used has been IFN-α monotherapy. In numerous studies of patients with MC and glomerulonephritis, monotherapy with IFN-α has been proved to decrease proteinuria and stabilize renal function [8, 11–13, 65, 70, 71]. Most studies showed a significant decrease in proteinuria in HCV-related membranoproliferative glomerulonephritis (MPGN) after IFN-α monotherapy [9, 12], while other authors did not obtain a response [11]. The effect of this therapy on renal function is discouraging, because there is no significant change in creatinine level [9, 11, 12]. Case reports of successful treatment with higher doses of IFN-α [72] have been published, and Yamabe et al. [65] have proposed increasing the dose of IFN-α to up to 10 million units daily for 2 weeks followed by 10 MIU every other day for 6 weeks.

The results of IFN-α monotherapy for HCV-associated MPGN may support the hypothesis that the therapeutic efficacy of IFN-α is closely related to its antiviral activity. Unfortunately, when treatment is ceased renal function frequently worsens again, often within 6 months to 1 yr [9, 11–13]. Some studies suggest that viral genotype and the disappearance of viraemia appear to predict the therapeutic outcome in patients with hepatitis C-associated renal disease [73–75].

Ribavirin monotherapy has also been used successfully to treat MC (with and without MPGN) in isolated cases [76, 77]. More recently, combination therapy has been found to be useful in cases that do not respond to monotherapy with either agent [23]. The treatment of HCV-related glomerulonephritis may include immunosuppressive therapy and corticosteroids [12, 78, 79]. A combination of IFN-α and steroids was used in one patient with cryoglobulinaemic MPGN, resulting in a marked improvement in the clinical and histological manifestations of the renal disease [78].

It appears that, in mild renal disease, IFN with or without low-dose steroids, is currently the best option. Treatment with IFN-α reduces proteinuria, suppresses viraemia and stabilizes renal function in chronic HCV infection, although patients often relapse after the cessation of therapy [12]. In patients with more severe disease, such as rapidly progressive glomerulonephritis or nephrotic syndrome with a rising creatinine level, a combination of antiviral agents, steroids, cyclophosphamide and/or plasmapheresis may be needed.

**Rapidly progressive glomerulonephritis**

In severe cases of MPGN or rapidly progressive glomerulonephritis, initial control of the inflammatory reaction with immunosuppressive drugs may be indicated, and severe cases of cryoglobulinaemic MPGN have been treated with corticosteroids combined with cyclophosphamide and/or plasmapheresis [80–83]. However, its effects on the underlying liver disease remains to be determined [82].

Isolated cases of coexisting cryoglobulinaemic and antineutrophil cytoplasmic antibody (ANCA) vasculitis have been reported in patients with chronic HCV infection. Lamprecht et al. [84] described two patients with chronic HCV infection, MC and ANCA, both with renal disease. In one patient, treatment with IFN-α (10 MIU three times a week) achieve a reduction in proteinuria (from 2.4 to 1.1 g/dl) and negativity for cANCA after 6 months of treatment. The second patient did not respond to prednisolone plus oral cyclophosphamide, and creatinine returned to normal values only after five sessions of plasma exchange.

**Membranous glomerulonephritis**

There are few studies on the management of patients with HCV-related membranous glomerulonephritis (MGN). Stehman-Breen et al. [70] described three patients with HCV-associated MGN treated with IFN-α. In two patients there was a striking decrease in proteinuria that coincided with a reduction in the circulating HCV RNA level. The third patient, whose initial underlying renal disease was more severe, suffered deterioration of renal function associated with increased ascites and oedema during IFN-α therapy, and eventually required haemodialysis.

**Neurological involvement**

**Peripheral neuropathy**

In contrast to other HCV-related extrahepatic manifestations, peripheral neuropathy (PN) does not respond as favourably to the different therapeutic regimes. In addition, it has been reported that IFN-α may cause a worsening of PN in patients with HCV MC, despite the improvement of hepatic function [85, 86]. Five recent studies have described the response of PN to different therapeutic options, including antiviral and immunosuppressive agents [24, 32, 34, 87, 88] (Table 3). Of the 30 cases of peripheral neuropathy in patients with chronic HCV infection in which a response to therapy was reported, only half presented a favourable response. IFN-α monotherapy resulted in improvement or stabilization in three patients, while another seven did

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**Table 2. Different therapeutic regimens used for treating HCV-related glomerulonephritis**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral therapy</td>
<td></td>
</tr>
<tr>
<td>IFN-α monotherapy</td>
<td>8, 11–13, 65, 70, 71</td>
</tr>
<tr>
<td>Ribavirin monotherapy</td>
<td>76, 77</td>
</tr>
<tr>
<td>Combined IFN-α + ribavirin</td>
<td>23</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>82</td>
</tr>
<tr>
<td>Cyclophosphamide + plasmapheresis</td>
<td>83, 84</td>
</tr>
<tr>
<td>Combined therapy</td>
<td>78</td>
</tr>
</tbody>
</table>

References

- Lamprecht et al. [84]
- Yamabe et al. [65]
- Stehman-Breen et al. [70]
- Other studies [23, 32, 34, 87, 88]

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not respond. Combination with corticosteroids and/or immunosuppressive agents did not improve PN in three patients. The best result was obtained when plasmapheresis was added to IFN-α and/or immunosuppressive agents, with improvement or stabilization in eight patients; two did not respond. Spontaneous stabilization without treatment was observed in three patients. Zuckerman et al. [24] used combined antiviral therapy (IFN-α plus ribavirin) to treat PN resistant to other therapies (IFN-α monotherapy, corticosteroids, immunosuppressive agents), and obtained stabilization or slight improvement in two of the four patients treated.

We suggest that the management of HCV-related PN should be based on its severity and response to treatment. Treatment with corticosteroids and/or IFN-α monotherapy should be considered as the best initial option in patients with slight to moderate neuropathy [89, 90]. In patients who do not respond, combined antiviral therapy or intravenous immunoglobulins should be considered. Plasmapheresis seems to be the best option in severe or refractory cases.

CNS involvement

Patients with chronic HCV infection may exceptionally present CNS vasculitis related to cryoglobulinaemia [91]. Dawson and Starkebaum [92] described one HCV patient with isolated cerebral vasculitis associated with cryoglobulinaemia who received an intravenous pulse of methylprednisolone, followed by oral prednisone (60 mg/day) and cyclophosphamide. Warfarin and IFN-α were added later, with substantial improvement of symptoms, and the patient was able to return to work 18 months after the onset of vasculitis.

Pulmonary involvement

There are few data on the treatment of pulmonary alveolitis in patients with chronic HCV infection [93, 94]. The severity of this situation suggests the need for aggressive treatment combining antiviral and immunosuppressive therapies and plasmapheresis. Our personal experience in one HCV patient with acute alveolitis was that treatment with IFN-α combined with intravenous pulses of methylprednisolone and cyclophosphamide resulted in improvement of pulmonary infiltrates, although progressive liver disease resulted in death.

Mucosal involvement

Sicca syndrome is a frequent finding in patients with chronic HCV infection. The main studies that include large series of patients [95] show that xerostomia is, on average, observed in 18% of HCV patients and xerophthalmia in 15%. Adequate management of sicca syndrome should include the replacement of oral and ocular fluids, practical advice to the patients about their sicca symptoms and their consequences, and a

### TABLE 3. Treatment of neuropathic involvement associated with chronic HCV infection: published studies

<table>
<thead>
<tr>
<th>First author Year</th>
<th>Sex, age (yr)</th>
<th>Anti-HCV therapy (duration)</th>
<th>Corticosteroids</th>
<th>Immunosuppression</th>
<th>Plasmapheresis</th>
<th>Outcome</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F, 22</td>
<td>IFN-α + ribavirin (6 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Slight improvement</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>F, 70</td>
<td>IFN-α + ribavirin (6 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No response</td>
<td>Anaemia</td>
</tr>
<tr>
<td></td>
<td>M, 60</td>
<td>IFN-α + ribavirin (6 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Slight improvement</td>
<td>–</td>
</tr>
<tr>
<td>Heckmann [88] 1999</td>
<td>F, 55</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Progression</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>F, 56</td>
<td>IFN-α monotherapy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Improvement</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>M, 62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Spontaneous stabilization</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F, 71</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Spontaneous stabilization</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Cacoub [34] 2001</td>
<td>n=1</td>
<td>IFN-α monotherapy (18–36 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Relapse</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>n=7</td>
<td>IFN-α monotherapy (6–12 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No response</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>n=1</td>
<td>IFN-α monotherapy (6–12 months)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>No response</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>n=1</td>
<td>IFN-α monotherapy (6–12 months)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>No response</td>
<td>–</td>
</tr>
<tr>
<td>Lidove [87] 2001</td>
<td>M, 78</td>
<td>IFN-α monotherapy (24 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>No response</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>M, 40</td>
<td>IFN-α monotherapy (24 months)</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Improvement</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>F, 62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Spontaneous stabilization</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M, 46</td>
<td>IFN-α monotherapy (10 months)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Improvement</td>
<td>Depression</td>
</tr>
</tbody>
</table>

CFM, cyclophosphamide; Aza, azathioprine.
multidisciplinary approach involving different specialties (odontology, ophthalmology, gynaecology, dermatology).

Thyroid involvement

Although chronic HCV infection is associated with a high prevalence of thyroid autoantibodies [96–98], only a few patients develop autoimmune thyroid dysfunction [99], and this association has not been clearly demonstrated in patients with chronic HCV infection not treated with IFN-α [100, 101]. Most HCV patients with thyroid dysfunction are middle-aged women with asymptomatic hypothyroidism and do not require specific treatment.

However, a more striking association of autoimmune thyroid disease in the setting of chronic HCV infection has emerged during IFN-α treatment. IFN-α therapy induces thyroid autoantibodies in patients with chronic HCV infection and may precipitate thyroid dysfunction in patients with pre-existing autoantibodies [102, 103], although biochemical abnormalities usually resolve after therapy ends [104, 105]. The management of IFN-α-induced thyroid dysfunction in chronic HCV infection remains a matter of debate. Some patients treated with thyroid medication before IFN-α treatment may require increased doses during therapy and decreased doses after IFN-α therapy has been completed [106, 107]. However, the presence of low titres of autoantibodies should not be regarded as a contraindication for IFN-α therapy. Because most patients with increased antibody titres or thyroid dysfunction (especially hypothyroidism) under IFN-α therapy recover after completing therapy, interruption of IFN-α therapy may not always be required, although treatment must be interrupted in patients with severe symptoms. Screening for autoantibodies and serum TSH is recommended before, during and after IFN-α treatment, and patients should be informed of the risk of thyroid dysfunction.

Systemic vasculitis

The most common form of vasculitis in patients with chronic HCV infection is cryoglobulinaemic vasculitis affecting mainly small vessels, although in some patients HCV-related vasculitis may not be due to associated cryoglobulinaemia [5]. Clinical manifestations can vary from mild skin disease (purpura, urticaria) and arthralgias to life-threatening renal, neurological or gastrointestinal involvement. In patients with features of cryoglobulinaemic vasculitis, an assessment of the nature and severity of organ involvement is essential before initiating therapy.

Interferon α monotherapy

In 1987, Bonomo et al. [108] began treating patients with type II cryoglobulinaemia with daily administration of IFN-α. After the identification of HCV, various studies analysed the effect of IFN-α monotherapy in the treatment of HCV-related cryoglobulinaemia. The current data come from prospective trials with relatively large numbers of patients [11, 13, 109–113]. These studies display considerable differences in the severity of target organ involvement, the underlying vasculitic process, the number of patients included, the dosage and duration of IFN-α treatment and the end-of-therapy or sustained response rates (biochemical and/or virological). Despite this heterogeneity, some important results have emerged. Treatment with standard doses of IFN-α produced a response rate ranging from 53 to 100% [11, 13, 109–113], although most patients had mild disease affecting mainly the skin (purpura) and joints (arthralgias). More severe involvement, such as renal and neural manifestations, was the most resistant to therapy. Moreover, when therapy was discontinued, a high relapse rate was observed, and although biochemical and virological responses were often seen at the end of therapy, sustained virological responses were observed in less than 20% of cases [9, 11, 13, 109–113]. Higher doses of IFN-α (3 MU/day for 3 months followed by 3 MU three times a week for 9 months) were associated with long-term clinical and virological response in an uncontrolled study by Casato et al. [111]. This regimen resulted in higher rates of alanine aminotransferase normalization than in previous studies, and disappearance of the clinical manifestations of MC (100 and 62% respectively). These results were accompanied by decreases in viraemia, anti-HCV antibody levels and cryocrit.

The disappearance of cryoglobulinaemic features after successful IFN-α therapy is closely related to the disappearance of HCV RNA from serum [8, 9, 11, 12]. In a controlled study by Misiani et al. [11] in patients with chronic HCV infection with severe symptomatic cryoglobulinaemia, HCV RNA disappeared in 60% of patients. Clinical and immunological manifestations improved only in these patients. However, after IFN-α cessation all patients suffered viral relapse, followed by recurrence or exacerbation of symptoms. Certain factors, such as low pretreatment cryocrit, HCV RNA level and genotype 2/3, have been associated with a better response to therapy [109, 114]. The study by Casato et al. [111], in spite of the small number of patients, suggests that HCV genotype 1 responds to IFN-α in the same way as genotype 2, as does the study by Zuckerman et al. [24]. As mentioned above, a clinical response to therapy is usually observed in patients who clear the circulating virus [11, 109], and the long-term response of the cryoglobulinaemic symptoms is closely associated with a sustained virological response [7, 8, 111]. Recent kinetic studies of patients with chronic HCV infection treated with IFN-α indicate that eradication of the virus requires both daily and extended (24–36 months) treatment [115, 116]. Patients with type II cryoglobulinaemia may need even longer treatment periods. Although the cryoglobulin level initially falls in tandem with the viraemia, undetectable levels of cryoglobulins (cryocrit <1%) may persist long after the apparent serum clearance of the virus [117]. The study by Casato et al. [111] and these new data on the viral kinetics of HCV suggest that prolonged daily administration of IFN-α should be considered in future therapeutic protocols.
Combined therapies

The successful use of ribavirin monotherapy has been reported in selected patients with HCV-associated MC [22, 76, 77, 118, 119]. Its use in combination with IFN-α has been evaluated recently in two studies. Donada et al. [120] studied the efficacy of IFN-α/ribavirin combination therapy in HCV patients with and without cryoglobulins, and found a reduction in cryocrit levels in patients with cryoglobulinaemia. Zuckerman et al. [24] treated nine patients with HCV-related cryoglobulinaemia (previously refractory to IFN-α monotherapy) with IFN-α and ribavirin, and found a substantial improvement in some MC-related symptoms but not in others. Arthralgia and/or arthritis resolved completely after 10 weeks of treatment in seven patients and improved in another, and vasculitic lesions disappeared in seven of eight patients and improved in the remaining patient. In the three patients with renal involvement, a substantial decrease in proteinuria was observed in one, a smaller decrease in another and no effect in the third. However, renal function was not normalized in any of the three patients. Polyneuropathy was resistant to treatment, although some improvement was observed in one patient after 4 months of combination therapy. MC symptoms recurred in four patients 6–9 months after cessation of treatment, but a second course of combination therapy achieved a favourable response similar to the first course.

Recently, Cacoub et al. [121] described the response to IFN-α and ribavirin therapy in 27 patients with chronic HCV infection and systemic vasculitis. This study demonstrated that treatment with combined IFN-α and ribavirin produced a complete clinical response in most patients, which correlated with the eradication of circulating HCV.

For patients with mild or moderate vasculitic symptoms, such as articular involvement or cutaneous vasculitis, IFN-α with or without ribavirin may suffice, but for patients with life-threatening organ involvement a combination of antiviral agents and immunosuppressive therapy is suggested, although there are few published data. Lamprecht et al. [32] reported an HCV patient with systemic involvement due to cryoglobulinaemia refractory to intravenous cyclophosphamide and oral corticosteroids that finally responded to plasmapheresis, higher doses of intravenous corticosteroids and oral cyclophosphamide. The age of the patient and reactive depression did not allow the introduction of antiviral therapy. The patient improved rapidly, with regression of her livedo reticularis, polyarthritis, paraesthesia and paresis.

Cacoub et al. [34] have recently analysed the outcome of 10 patients with HCV PAN-type vasculitis, five treated with a combination of prednisone (1 mg/kg/day) and plasma exchanges (12 sessions), and five with IFN-α (3 MIU three times a week for 18–36 months). All patients showed substantial neurological and physical improvement, with normalized blood pressure and regression of ischaemic abdominal pain, purpuric skin

### Table 4. Main therapeutic options for the management of extrahepatic manifestations associated with chronic HCV infection

<table>
<thead>
<tr>
<th>Extrahepatic condition</th>
<th>Therapeutic options</th>
<th>Refractory or severe cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias</td>
<td>Paracetamol</td>
<td>NSAIDs [33]*</td>
</tr>
<tr>
<td></td>
<td>Anti-COX-2</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>NSAIDs [33]*</td>
<td>Azathioprine [33]</td>
</tr>
<tr>
<td></td>
<td>Low-dose prednisone [33, 42]</td>
<td>IFN-α [42, 43]</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine [42]</td>
<td></td>
</tr>
<tr>
<td>Myositis</td>
<td>Prednisone [33, 35, 48]</td>
<td>IVIG [35]</td>
</tr>
<tr>
<td></td>
<td>IFN-α monotherapy [35]</td>
<td></td>
</tr>
<tr>
<td>Cutaneous vasculitis</td>
<td>Paracetamol</td>
<td>High-dose prednisone</td>
</tr>
<tr>
<td></td>
<td>Low-dose prednisone</td>
<td>Pulsed cyclophosphamide</td>
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<td></td>
<td></td>
<td>IVIG</td>
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<td></td>
<td></td>
<td>Prostacyclins</td>
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<tr>
<td></td>
<td></td>
<td>High-dose IFN-α [72]</td>
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<tr>
<td></td>
<td></td>
<td>Plasmapheresis [82]</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>IFN-α monotherapy [8, 11, 13, 65, 70,71]</td>
<td></td>
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<tr>
<td></td>
<td>Ribavirin monotherapy [76, 77]</td>
<td></td>
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<tr>
<td></td>
<td>IFN-α + ribavirin [23]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisone [78, 79]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFN-α + prednisone [78]</td>
<td></td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>IFN-α monotherapy [70]</td>
<td>Plasmapheresis [32, 34, 87]</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Prednisone [32, 34, 88]</td>
<td>Cyclophosphamide [32]</td>
</tr>
<tr>
<td></td>
<td>IFN-α monotherapy [34, 87, 88]</td>
<td></td>
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<tr>
<td></td>
<td>IFN-α + ribavirin [24]</td>
<td></td>
</tr>
<tr>
<td>CNS involvement</td>
<td>High-dose prednisone [92]</td>
<td>Plasmapheresis [93]</td>
</tr>
<tr>
<td></td>
<td>Pulsed cyclophosphamide [92]</td>
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<tr>
<td>Pulmonary alveolitis</td>
<td>High-dose prednisone [93]</td>
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<td></td>
<td>Pulsed cyclophosphamide [94]</td>
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<td></td>
<td>Ribavirin monotherapy [22, 76, 77, 118, 119]</td>
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<td></td>
<td>IFN-α + ribavirin [34, 120, 121]</td>
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<td>Prednisone [24]</td>
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*IVIG, intravenous immunoglobulins; CNS, central nervous system.

*Requires individual evaluation.
lesions and fever. One patient presented a relapse of PAN after cessation of IFN-α, which rapidly responded to plasmapheresis, IFN-α, ribavirin and low-dose steroids, with resolution of viraemia and remission of vasculitis.

In spite of the small number of patients in the studies by Zuckerman et al. [24] and Cacoub et al. [34, 121], it may be concluded that, in selected patients with severe and/or refractory HCV-related cryoglobulinaemia, combined antiviral therapy plus corticosteroids and/or immunosuppressive agents may give symptomatic relief and even long-term remission of the cryoglobulinaemic syndrome. In severe, symptomatic cryoglobulinaemic vasculitis, plasmapheresis should also be considered [122, 123]. The optimum length of treatment remains to be established, and severe cases may need long-term or even lifelong therapy.

Conclusions
The optimal treatment strategy for HCV-related extrahepatic manifestations remains to be defined. Because few data are available, more information is needed before definitive therapeutic recommendations for these extrahepatic HCV features can be established. The therapeutic guidelines for extrahepatic HCV features should be based on clinical features rather than on the underlying pathogenic mechanisms. However, both antiviral and immunosuppressive therapies, either alone or in combination, seem likely to have an important role, although these treatments should be administered with caution. The exacerbation or precipitation of autoimmune symptoms should be monitored closely. Combined antiviral therapy also appears to be effective in treating symptomatic disease, although the relapse rate after discontinuation is high. Conventional corticosteroid therapy, immunosuppressive agents, intravenous immunoglobulins and/or plasmapheresis should be added in specific severe or refractory cases. When long-term immunosuppressive therapy is anticipated, the addition of combined antiviral treatment is specially indicated: this requires very close monitoring of liver function, HCV RNA levels and cell counts. Treatment should be individualized according to cost, follow-up, relapses, organ involvement, risk of exacerbation of autoimmune disease and the possible consequences of immunosuppression in the setting of chronic HCV infection. Table 4 lists the most common HCV-associated extrahepatic manifestations and possible treatment options. The search for new antiviral treatments, possibly combined with immunosuppressive agents, is urgently needed because of the significant morbidity and mortality associated with these manifestations. Hopefully, further research will establish a safe and effective regimen for treating HCV-related extrahepatic features.

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