

Treatment of Patients Infected with Hepatitis C Virus and Presenting Extrahepatic Manifestations

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HCV and Mixed Cryoglobulinemia

Antiviral treatment should be performed with the same medications (standard or pegylated interferon alpha (PEG-IFN- α , with or without ribavirin) and similar regimens, until additional controlled studies provide further information on the treatment of mixed cryoglobulinemia (MC) related to infection with the hepatitis C virus (HCV).

Data regarding antiviral treatment of MC (Table 1) show that this therapeutic approach should be the first choice due to the antiproliferative and immunomodulatory effects of IFN and the usefulness of antiviral treatment, as demonstrated in most studies. In addition, the strict correlation between virological and clinical response, as well as the positive effect of inhibiting viral replication in the expanded B-cell clones, which is considered the pathogenic basis of MC, are reasons to make this choice. However, IFN- α can also trigger or worsen autoimmune diseases [6,7].

Renal insufficiency and neuropathies can occur or be worsened, and ulcer cicatrization may be prolonged. Therefore, treatment with IFN- α should be restricted to symptomatic patients, with or without renal involvement, after the careful evaluation of clinical and laboratory characteristics regarding autoimmunity during this period.

In comparison with the antiviral treatment of chronic hepatitis C, the antiviral treatment of MC is more complex due to various reasons, such as the lack of standardized treatment protocols, the higher incidence of recurrence and the contraindications to antiviral treatment (old age, severe hepatic disease, acute nephritis and disseminated vasculitis). In

addition, the interpretation of laboratory findings seems to be more complex than in chronic HCV infection. In fact, biochemical markers of MC response (cryocrit, rheumatoid factor or complement activity) can be more independent of the virological response than are alanine aminotransferase (ALT) levels.

At the moment, antiviral treatment is suggested as the treatment of choice for this condition, even when there is no indication of hepatic pathology. Patients with apparently benign manifestations of the disease (palpable purpura, arthralgia and mild fatigue) should not be treated or can be symptomatically treated with nonsteroidal anti-inflammatory drugs. Special attention must be given to the treatment of patients with severe MC (with acute nephritis and disseminated vasculitis). For these cases, the data are insufficient to guarantee the safety of IFN administration, and we therefore strongly suggest a cautious approach. It is preferable to use an alternative therapeutic approach to all patients for whom antiviral treatment is contraindicated or not tolerated, as well as for those who did not respond to previous treatment. Possible alternatives include the use of corticosteroids, immunosuppressants, plasmapheresis and a hypo-antigenic, or low-antigen-content, diet [8].

Treatment should be individualized for each patient according to the severity of clinical symptoms, considering other factors involved (age, comorbidities, etc.) and for a limited period of time (weeks or months) until the remission of symptoms. Any therapeutic approach must be avoided for clinically asymptomatic patients.

Table 1. Therapeutic regimens used for mixed cryoglobulinemia associated with hepatitis C virus infection

Author	Year	Number	Treatment (months)	Treatment duration response	End-of-treatment	Sustained virological response
Zuckerman [1]	2000	9 NR	3 MIU IFN 3 \times /week +RBV	6	78%	NA
Mazzaro [2]	2003	27 NR or Relapsers	3 MIU IFN 3 \times /week +RBV	12	85%	NA
Alric [3]	2004	18	3 MIU IFN 3 \times /week or PEG-IFN + RBV	\geq 18	NA	70%
Cacoub [4]	2005	9	1.5 μ g/kg/week PEG-IFN +RBV	\geq 10		88%
Mazzaro [5]	2005	18	1.0 μ g/kg/week PEG-IFN +RBV	12	89%	44%

CS: corticosteroid; NR: Nonresponders; IFN: interferon; PEG: pegylated; RBV: Ribavirin; NA: not available.

Prior to the identification of HCV, corticosteroid therapy was the treatment of choice for MC, since corticosteroids, even in small doses, control most of the symptoms. However, corticosteroids can favor HCV replication, cause various side effects and not induce significant changes in the cryocrit or in the natural history of the disease. Cytostatic, immunosuppressive drugs (e.g., cyclophosphamide, chlorambucil and azathioprine) are mainly used, in combination with plasmapheresis, when there is no response to corticosteroids and during acute phases of MC (acute nephritis evolving to renal insufficiency and hyperviscosity syndrome). Various studies showed that rituximab (anti-CD20 antibody, a specific B-cell surface antigen) is efficacious for most patients with MC, with the significant improvement or resolution of MC – particularly skin lesions – and regression of clonal expansion of B cells [9].

Plasmapheresis is indicated for the removal of circulating cryoglobulins and immunocomplexes.

Due to its efficacy and fast action, plasmapheresis is especially recommended in the presence of acute manifestations (cryoglobulinemic nephritis, severe sensory-motor neuropathies, skin ulcers and hyperviscosity syndrome). Combined with cyclophosphamide, it has been shown to effectively reduce the rebound effect at the end of apheresis. The low-antigen-content diet has low macromolecule content with high antigenic properties, resulting in more efficient removal of cryoglobulins by the reticuloendothelial system. This diet can improve the minor manifestations of the disease (purpura, arthralgia and paresthesias) and is generally prescribed during the initial phase of the disease.

HCV and Lymphoma

The inclusion of antiviral treatment seems to be rational in therapeutic regimens for non-Hodgkin's lymphomas (NHLs) and HCV infection. This approach is supported by recent studies on low-grade lymphomas [10], and, in particular, on marginal zone lymphomas [11,12].

Vallisa et al. [10] treated 13 patients diagnosed with concomitant low-grade NHL-B and HCV infection, characterized by an indolent evolution, with PEG-IFN and ribavirin. A hematologic response was seen in most patients (complete and partial response, 75%), and this was strongly associated with the clearance or reduction of HCV viral load in serum, after the treatment, which proved to be useful for treating this pathology.

Hermine et al. [11] reported that patients with concomitant HCV infection and splenic lymphoma with villous lymphocytes presented complete remission after being treated with IFN. The inclusion of a control group with patients diagnosed with the same disease but presenting no HCV infection demonstrated that, unlike the patients with HCV infection, the HCV-negative patients did not respond to the treatment with IFN. Similarly, remission of polyclonal proliferation in response to the antiviral treatment proved to be clearly associated with virological response [13].

Although antiviral response seems to be an attractive tool for low-grade NHL and positive HCV, chemotherapy might be necessary for intermediate- or high-grade NHL, and the antiviral treatment can be maintained after chemotherapy [14]. The use of rituximab in NHL associated with HCV, alone or in combination (with antiviral treatment or with chemotherapy), seems very promising, especially for low-grade NHL [15-17]. Despite the limited number of described cases, it is reasonable to consider rituximab a safe and efficacious treatment for indolent B-cell lymphomas accompanied by HCV infection.

HCV and the Presence of Autoantibodies

From a clinical point of view, the major concern is represented by the use of IFN. It has been reported that the administration of IFN can have a negative effect on autoimmune hepatitis. Significant increases in ALT activity – even if transitory, corrected with corticosteroids and not associated with deterioration of liver function – have also been reported in HCV/anti-liver-kidney-microsomal type 1 (anti-LKM1)-positive cases treated with IFN [18,19].

Initial treatment for CS is recommended when there are high antibody titers ($\geq 1:320$), high globulin titers, anti-LKM1 antibodies, anti-human microsomal cytochrome P450 (CYP) IID6 257-279 antibodies and interface hepatitis with various plasmocytes. In the case of initial treatment with IFN, rigorous monitoring of ALT levels is suggested, especially in patients who are anti-LKM1-positive.

HCV and Sjogren's Syndrome

In one study, 12 patients diagnosed with concomitant Sjögren's syndrome and HVC infection were treated with IFN alone or with the combination of IFN and ribavirin [20]. Half of the patients presented improvement of the dry syndrome using the associated regimen, but none responded to IFN in isolation. Various patients presented adverse immunologic events during treatment.

HCV and Arthritis

Treatment decisions must be made case by case. Etiologic treatment with IFN- α and ribavirin is recommended when there is hepatic or systemic involvement, since it can occasionally induce or worsen autoimmune disturbances. The treatment leads to a significant improvement in HCV-related arthritis, even without a complete biochemical or virological response. Cryoglobulinemia-related arthritis generally responds to antiviral treatment. Considering there are few data available at the moment, the usually non-aggressive evolution of HCV-related arthritis does not justify the use of antiviral medications as a standard treatment.

HCV and Porphyria Cutanea Tarda

Treatment with IFN- α seems to be less efficacious in patients with concomitant chronic HCV infection and porphyria cutanea tarda than in those with chronic HCV infection alone. [21]. The disease also responds to iron

depletion by phlebotomy, which can be performed prior to antiviral treatment. However, porphyria can be triggered in genetically predisposed patients treated with the association of IFN- α and ribavirin, as a consequence of hemolysis induced by ribavirin, which causes an increase in serum iron levels [22].

HCV and Lichen Planus

Doutre et al. [23] reported improvement in lesions of two patients treated with IFN- α . Other authors [24-28] also reported that lesions disappeared during treatment with IFN- α for several months after the end of treatment. Protzer et al. [29] reported oral and cutaneous lichen planus (LP) exacerbations during the treatment with IFN- α . Treatment was discontinued because local measures did not improve the lesions.

It is generally recommended that stricter control measures be taken when patients with previous manifestations of LP receive IFN. There are no detailed reports on the effect of the combination of IFN and ribavirin in patients with concomitant LP and HCV infection.

HCV and Thyroid

The treatment with IFN- α may trigger the formation of autoantibodies in patients with HCV and exacerbate thyroid dysfunction in patients with pre-existing antibodies [30-33]. Changes are generally detected after three months of treatment and disappear when treatment is discontinued [34].

In severe cases, treatment must be discontinued, particularly in patients with hypothyroidism. Alternatively, in patients previously receiving thyroid medications, it can be useful to increase the dose during the antiviral treatment [35]. Low antibody titers are not an indication for treatment discontinuation. The possibility of good treatment control generally allows the continuity of antiviral treatment. Prior to treatment, levels of thyroid hormones, including thyroid-stimulating hormone (TSH), as well as anti-thrombopoietin antibodies, must be monitored. In addition, it is opportune to perform regular TSH monitoring during treatment. When there are altered values, the decision of continuing or discontinuing the treatment must be made case by case.

HCV and Type 2 Diabetes Mellitus

Considering that hyperglycemia was considered an independent risk factor for the 'nonresponse' to antiviral treatment of chronic hepatitis C [36], and that abnormal glucose levels can be associated with host-related factors, such as age, gender, alcohol use, ethnicity, obesity and resistance to insulin, it is recommended that glucose levels in blood be controlled (by means of medications or changes in lifestyle), prior to the administration of antiviral treatment.

HCV and Nephropathies

The treatment options for HCV and nephropathies are essentially the same as those described for MC [37-40].

However, during the acute phase of kidney disease (when renal insufficiency and systemic manifestations are present), it is recommended that antiviral treatment be avoided or discontinued. In this case, measures aimed at reducing the inflammatory activity of renal lesions (corticosteroid therapy), removing circulating cryoglobulins (plasmapheresis) and reducing the formation of new antibodies (cyclophosphamide administration) are used [41-45]. Under these conditions, favorable outcomes have been achieved with mycophenolate mofetil and, more recently, with anti-CD20 antibody (rituximab). Regarding the use of ribavirin, lower proteinuria and improved kidney function have been reported in patients treated with IFN + ribavirin [1, 46,47]. It must be highlighted that ribavirin clearance is reduced in patients with renal insufficiency, and that dialysis does not eliminate the medication. Therefore, the use of this antiviral drug in standard doses is not recommended for patients who present with creatinine clearance < 50 mL/min.

HCV and Neuropathies

Treatment with IFN- α is not efficacious and can worsen peripheral neuropathy in patients with chronic hepatitis C and MC [48]. A detailed review of available studies on patients with both HCV infection and peripheral neuropathy was inconclusive. There were patients who responded to corticosteroids, endovenous immunoglobulin or plasmapheresis combined with antiviral treatment [49].

HCV and Resistance to Insulin

When treating patients with HCV infection, the physician has the challenge of differentiating patients with good prognoses from those with poor prognoses, especially regarding the intervention measures available. At the moment, the available data allow us to infer that the treatment of insulin resistance (reducing hyperinsulinemia) and of those factors that surely contribute to the onset and maintenance of steatosis can increase the rate at which a sustained virological response is achieved in patients with HCV infection who were treated with the combination of PEG-IFN and ribavirin.

Comments

Decisions regarding the treatment of the abovementioned pathologies must be taken on a case-by-case basis, since the pathogenesis of most of these clinical manifestations are unknown. Cumulative knowledge on each of the pathologies must be considered regarding the immunomodulatory effect of IFN- α , which is the standard treatment for HCV infection. One option would be the use of an immunosuppressive agent in conjunction with interferon when there are autoimmune phenomena.

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