ABSTRACT

Doctorate: Etiopathogenesis in hematologic modifications on patients with viral chronic hepatitis under antiviral treatment.

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KEYWORDS: Antivira therapy, Chronic hepatitis, Neutropenia, Anemia, Thrombocytopenia, Hematologic abnormalities, Sindromul Sjogren, non-Hodgkin lymphoma.
DOCTORATE SYNTESIS

Introduction

More than 4 million people in the United States are infected with hepatitis C virus (HCV). During the next 20-30 years, the burden of HCV-related mortality and morbidity will likely double. Hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia are common during combination therapy with pegylated (or standard) interferon and ribavirin for chronic hepatitis. The clinical implications of neutropenia or thrombocytopenia are less clear than for anemia; nevertheless, severe infection and bleeding are uncommon. Dose adjustments effectively treat these hematologic side effects, but the resulting suboptimal dosing and potential impact on virologic response are major concerns. Recent attempts to maximize adherence to the optimal treatment regimen have used hematopoietic growth factors rather than dose adjustment to treat side effects.

Interferon and ribavirin combination therapy for chronic hepatitis C produces a number of well-described side effects that are dominated by fatigue, influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Hematologic side effects are particularly common; bone marrow suppression caused by interferon may result in neutropenia and thrombocytopenia. Ribavirin is directly toxic to red blood cells and is associated with hemolysis, which is usually dose-related but self-limited.

Hematopoietic growth factors may provide a useful alternative for managing these hematologic side effects without reducing the optimal dose of the combination antiviral regimen. Therefore, there is increasing emphasis on the use of growth factors such as filgrastim and erythropoietin to stimulate bone marrow production of erythrocytes and leukocytes to allow patients to receive the optimal doses of interferon and ribavirin.

Material and methods

The study included 127 patients who receive antiviral treatment by present protocols. Patients are distributed in two groups:

- 63 patients - 39 male and 24 female, diagnostics with chronic hepatitis C and combinations chronic hepatitis B and C (with virus C activity) - in group PRIN. They receive combination therapy with PEG-IFN and ribavirin. (table 1).
- 64 patients – 38 male and 26 female, diagnostics with chronic hepatitis B and combinations chronic hepatitis B and D, B and C (with virus B activity) – in group IN. They receive interferon in monotherapy.
Hematologic abnormalities under the therapy was monitored by analyzed hematologic cells (erythrocytes, leucocytes and thrombocytes) and their characteristics initial and under antiviral therapy.

**Particularity of study**

Chronic hepatitis C virus infection (CHCV) has high prevalence of immunological abnormalities. Extrahepatic manifestations (EHM) have been reported in association with CHCV infection, whose heterogeneity makes difficult any correlation between the two disorders. Among extrahepatic symptoms of C virus hepatitis, sicca syndrome (SS) is also registered. Sjögren or sicca syndrome is a chronic, slowly progressive disease, with inflammatory-immune mediation characterized by lymphocytic infiltration of the lachrymal and salivary glands. A distinct primary form and a secondary one, occurring when presented in the context of an autoimmune or hepatic disease have been described. We present a case of SS in a patient with CHCV, commenting a possible link between primary SS and the CHCV, as well as the similarities and the distinctions among these conditions.

The case presented by us totally corresponds to the description of Sicca Syndrome in HCV infected patients. However it distinguished through in at least two aspects. First, the setting of Sicca syndrome symptomatology prior to the hepatic one, suggesting the effectuation of investigations with the purpose of decelerating a potential HCV infection and its confirmation. Second, something which is extremely important to us, the amelioration of salivary and ocular symptomatology following interferon and ribavirina therapy, which, undoubtedly can sustain the implication of HCV viral infection in developing Sicca syndrome.

Our conclusion is that CHCV can induce SS with some clinical particularities like presence of pericapillary and not pericanalicular lymphocytic infiltrate without destroying the salivary glands, in the absence of SS-A/SS-B antibodies. The favorable evolution of SS under IFN therapy is an argument for an authentic relation. Further studies are necessary to determine if CHCV is an etiological agent of SS or of it can induce a pseudo-sicca syndrome, characterized by a simple glandular inflammation consisting mainly in a simple lymphocytic adenitis.

**Conclusions**

Dose adjustments effectively treat these hematologic side effects, but the resulting suboptimal dosing and potential impact on virologic response are major concerns. Recent attempts to maximize adherence to the optimal treatment regimen have used hematopoietic growth factors rather than dose adjustment to treat side effects. Research on growth factor support has focused on anemia and neutropenia.
Hematologic side effects (anemia, neutropenia, and thrombocytopenia) of combination therapy with pegylated (PEG)-interferon alfa and ribavirin are commonly encountered during antiviral therapy for chronic hepatitis C (HCV). An important consequence of these side effects is dose modification of PEG-interferon alfa, ribavirin, or both. Dose modification (including discontinuation) diminishes the efficacy of optimal treatment regimen for HCV and may have a negative impact on sustained virologic response. Additionally, fatigue associated with anemia may impair patients' quality of life. The clinical implications of neutropenia or thrombocytopenia are less clear than for anemia; nevertheless, severe infection and bleeding are uncommon. Dose adjustments effectively treat these hematologic side effects, but the resulting suboptimal dosing and potential impact on virologic response are major concerns.

In this study conclusions was:

- Bone marrow suppression caused by interferon result anemia and low value of reticulocytes.
- Blood examination detected rare erythrocytes in correlation with anemia degree and the erythrocytare morphology show anizocytozis, anizocromia with hipocromia and poikilocytozis.
- Bone marrow examination indicate hiporegeneration on the cells.
- In this study, analizyng the parameters, no indicate autoimunity fenomen. The iron value was normal, erythrocytar parameters reveal a normocrom anemia, normal erythrocytar volume and low erythrocytare hemoglobin value.
- In group IN, the degree of hemoglobin was lower in order to decrease in patients with chronic hepatitis with both virus B and C (with virus B activity), then in patients with virus B associated with virus D, and the most higher value of hemoglobin was in patients with virus B infection only.
- This results reveal the agression of asociated virus infection on the liver and on the hemoglobin value.
- The lower value of hemoglobin and erythrocytes was more pronounced in women group than men group, although the lower value of hemoglobin was isolated on male pacient with virus associated hepatitis B and C (10,5 g/dl) in group IN.
- Serum examination reveal normal iron value and toxic mechanism to red blood cells induced hemolysis by ribavirin.
- It was not possible to investigate: serum haptoglobin, urine hemoglobin (marker of hemolysis), urine hemosiderin, spleen scintigraphy.
- Hepatitis C virus infection has been associated with the formation of auto antibodies. Further more, several autoimmune and immune complex mediated disorders have been
proposed to be associated with hepatitis C virus infection. Antinuclear antibodies was normal on five patients.

- The reticulocytes value was low because of bone marrow suppression caused by interferon.
- In group of patients PRIN the value of hemoglobin do not was lower in patients with combined virus infection B and C, than monoinfection with virus C.
- The liver biopsy examined by coloration with HE and van Gieson showed a predominant inflammatory infiltration of the portal tracts. This infiltrate consisted primarily of lymphocytes with variable plasma cells and macrophages and occasionally a few neutrophils or eosinophils. The lymphocytes were organized into lymphoid follicles, sometimes with germinal centers. Most portal tracts were involved to some extent, but the intensity of involvement ranged from a sparse collection to a dense crowding of the portal tract; some portal tracts were spared. Bile ductular proliferation was also noted, generally of mild degree, with damaged interlobular bile as manifest by epithelial swelling, vacuolation, and inflammatory infiltration.

The impact of growth factors on sustained virologic response and their cost-effectiveness in patients with chronic hepatitis C need further assessment.

Although this early work shows tremendous promise for managing hematologic side effects of combination therapy for HCV, and potentially enhancing adherence, further research is needed to clarify the efficacy, safety, and cost-effectiveness of growth factors in the management of patients with chronic HCV.

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