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Indications for treatment in chronic HCV infection

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ABSTRACT

HCV Infection is a global burden disease and it is related to the development of progressive liver fibrosis, cirrhosis and hepatocellular carcinoma. At least 80% of the persons that have an acute infection evolve to chronicity. This event affects the patient and their contacts for the risk of acquiring the infection. Once chronic HCV is present some factors accelerate progression: older age, obesity, alcohol consumption, etc. Severity of fibrosis is one of the most important factors to be analyzed before deciding to treat a patient. Pegylated interferon and ribavirin is the "standard of care" for this disease, however, it has many side effects, some of them life threatening. That is the reason why this treatment must be indicated in the right moment in the right patient. A complete medical evaluation must be done previously to initiate treatment. Other concurrent problems must be ruled out or treated. Decompensated cirrhosis, autoimmune diseases or other uncontrolled disease are contraindication to HCV treatment. Previous failure to treatment for HCV must be analyzed to identify the reasons for that event and consider retreatment. Cryoglobulinemia and membranoproliferative glomerulonephritis are indications for treatment independent from the severity of liver disease.

Key words. Hepatitis C infection. Treatment. Crioglobulinemia. Glomerulonephritis.

INTRODUCTION

HCV infection is considered a global burden disease.[1] All epidemiological studies have demonstrated that there are approximately 180 million persons already infected worldwide, and that this infection is the principal cause of death from liver disease and the leading indication for liver transplantation in some countries. Some calculations suggest that mortality related to HCV infection (death from liver failure or hepatocellular carcinoma) will continue to increase over the next two decades.[2-4]

In Latin-America, the real prevalence is not known, but some studies suggest that it may be between 1 to 2.6 percent, depending on the country evaluated and even inside each country there are regional differences.[5]

The problem with hepatitis C infection is that the majority of persons that are infected will develop chronic disease. After some time a variable degree of liver inflammation, progressive fibrosis, even cirrhosis, will develop as well as hepatocellular carcinoma (HCC).[6-8] In order to that, HCV infection should be treated to avoid chronic liver disease as well as HCC, additional benefits will be improving quality of life and survival.

Fortunately, at the moment the combination of pegylated interferon and ribavirin is the "standard of care" for this disease. Genotype, time of infection, gender, fibrosis degree, alcohol intake, and comorbidities are some factors that are related to viral response.[9] In addition, the consequences of using these drugs might be deleterious in certain cases (i.e autoimmune disease, epilepsy, cardiovascular problems, cirrhosis, etc.). In order to that, it is very important to choose the right moment in the right patient to treat this disease.

WHY SHOULD WE TREAT PATIENTS WITH HCV CHRONIC INFECTION?

There is a lot of evidence demonstrating that 55% to 85% of individuals who develop acute hepatitis C will remain infected.[10-11] Chronic HCV infection is relevant for the infected persons as well as for their contacts: the former are at risk for progression to ci-

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rrhosis and/or HCC, and the latter are at risk of acquiring the infection through exposure to the virus.

The risk of developing cirrhosis ranges from 5% to 25% over periods of 25 to 30 years.[12-13] However prospective studies of women and children report lower rates, 1% to 3%.[14-15]

Once chronic hepatitis C is present, progression to cirrhosis may be accelerated in persons who are of older age, obese, immunosuppressed, and in those who consume more than 50 gr. of alcohol per day.[16-19]

At the moment, the preferred approach to assess the degree of fibrosis is liver biopsy, using a validated staging system such as the Ishak or Metavir systems. Persons with no or minimal fibrosis have a low risk for liver-related complications and liver-related death. However, the presence of bridging fibrosis is an important predictor of future progression to cirrhosis and therefore an indication for treatment.[20]

Infection with HCV can also cause extrahepatic diseases including mixed cryoglobulinemia, types II and III. Indeed, symptomatic cryoglobulinemia is an indication for HCV antiviral therapy regardless of the stage of liver disease. The same happens with glomerulonephritis induced by hepatitis C virus.

Treatment Goals

The goal of therapy is to prevent complications and death related to HCV infection. Because of the slow evolution of chronic HCV infection, treatment responses are defined by biochemical, virological or histological parameters:

- Normalization of serum ALT levels.
- Absence of HCV RNA from serum by a sensitive PCR based assay.
- Improvement in at least 2 points in the necroinflammatory score with no worsening in fibrosis score.

Pretreatment Predictors of Response

Pretreatment predictors of response are useful for advising patients on their likelihood of an SVR. The two major predictors of a SVR are viral genotype and pre-treatment viral load.

Other less consistently favorable factors include female gender, age less than 40 years, non–African-American race, lower body weight (< 75 kg), absence of insulin resistance, elevated ALT levels (three-fold higher than the upper limit of normal), and absence of bridging fibrosis or cirrhosis on liver biopsy.[21-23]

Selection of Patients for Treatment

Current recommendations for treatment of persons of chronic HCV infection derive from randomized clinical trials.[21-23] However in the last years it has been demonstrated that in patients with normal ALT levels treatment is equally effective.[24,25] More data is needed in patients with renal disease, depression, children, and those with HIV/HCV co-infection. As a general recommendation a balance must be done between the benefit and risk related to therapy, and always discussing this topic with the patient.

Assessment Prior to Therapy

It is mandatory to assess liver status. If cirrhosis is present it must be determined if it is compensated or not, as well if portal hypertension is present.

As treatment has high risk to induce severe side effects it is advisable to assess the risk of underlying coronary heart disease and control preexisting medical problems, such as diabetes, hypertension, asthma, COPD, screening for common cancers, and evaluate symptoms of depression prior to initiating therapy[26,27] (Table 1).

Retreatment in those Who Failed to Respond to Previous Treatment

Unfortunately we still do not have the ideal treatment for all cases of chronic HCV infection. There are patients who never respond, have a

Table 1. Common characteristics of patients for whom therapy is accepted.

- Age 18 to 70 years old.
- HCV RNA positive in serum.
- Liver biopsy: chronic hepatitis with significant fibrosis (bridging fibrosis or higher).
- Compensated liver disease:
  - Absence of gastro-esophageal varix.
  - Total serum bilirrubin below 1.5 g/dL.
  - INR below 1.5.
  - Serum albumin higher than 3.4 .
  - Platelet count 75,000 mm.
  - No evidence of hepatic decompensation (hepatic encephalopathy or ascites).
- Hemoglobin 13 g/dL for men and 12 g/dL for women.
- Neutrophil count 1500/mm^3.
- Serum creatinine below 1.5 mg/dL, and
- Willing to be treated and to adhere to treatment requirements.
- No contraindications.

Table 2. Contraindications for HCV treatment.

- Major and uncontrolled depressive illness, or other mental disease.
- Solid organ transplant (renal, heart, or lung).
- Autoimmune conditions known to be exacerbated by peginterferon and ribavirin.
- Untreated thyroid disease.
- Pregnant or unwilling to comply with adequate contraception.
- Severe concurrent medical disease such as hypertension, heart failure, coronary heart disease, uncontrolled diabetes, chronic obstructive pulmonary disease, and epilepsy.
- Age less than 2 years.
- Known hypersensitivity to drugs used to treat HCV infection.

Table 3. Characteristics of persons for whom therapy should be individualized.

- Failed prior treatment: identifying reasons for such failure.
- Addicts to drugs or alcohol. Candidates should be abstinent for a minimum of 6 months.
- Liver biopsy demonstrates either no or mild fibrosis.
- Acute hepatitis C.
- Coinfection with HIV.
- Under 18 years of age.
- Chronic renal disease, with or without dialysis.
- Liver transplant recipients.

breakthrough or relapse. The approach in any of these cases depends on:

- Nature of the initial response.
- Potency of initial treatment.
- Viral factors.
- Host factors, poor adherence to the prescribed treatment and inappropriate dose reductions can contribute to poor response rates.

Non-Responders

Approximately thirty percent of patients treated with pegylated interferon and ribavirin are unable to clear virus from the serum.[21,22] It is also known that retreatment with the same regimen leads to a SVR in fewer than 5% of patients and therefore cannot be recommended.[28]

HALT-C trial, designed in order to prevent progression of liver fibrosis induced by hepatitis C virus has demonstrated that maintenance therapy with peginterferon in order to delay or prevent progression to cirrhosis is not useful.[29] Therefore it is not recommended.

For non-responders to standard interferon either with or without ribavirin, retreatment with Peginterferon alfa-2a or 2b has been demonstrated better responses, 20-40%. It must be assessed carefully to initiate therapy in these cases.[30,31]

Relapsers

Patients with virological relapse are likely to respond to the same regimen given a second time but will still experience an unacceptable rate of relapse. The selection of the patients must take into account host and viral factors. During retreatment, rapid viral response, and early viral response are fundamental to decide the time of treatment.[32]

What to do with patients with Normal Serum Aminotransferase Values?

While on average, persons with persistently normal ALT values have significantly less liver fibrosis than persons whose ALT levels are abnormal, there are reports of marked fibrosis (5%-30%) and even cirrhosis (1.3%) in persons with normal ALT values.[33-35] Thus, it is evident that HCV-infected persons with normal ALT values do need treatment if the liver biopsy shows significant fibrosis. Moreover, there are multiple studies that report SVR rates with standard-of-care treatment that do not differ from those achieved in persons with abnormal enzymes, and that treatment is equally as safe.

What to do with patients that have other diseases related to HCV infection?

Infection with HCV may be associated with the development of a many extrahepatic disorders, being the most serious essential mixed (type II) crioglobulinemia,[36-38] and glomerulonephritis associated to HCV infection.[39-41]

Typical feature of crioglobulinemia is a systemic vasculitis: palpable purpura, arthralgias and arthritis, fatigue, peripheral neuropathy, and glomerulonephritis. Since the early presentation of crioglobulinemia may consist simply of proteinuria and renal dysfunction without symptoms, all persons with proteinuria and crioglobulinemia should be screened for HCV RNA.

Treatment of cryoglobulinemia-associated glomerulonephritis is challenging, and this should be restricted to those with overt symptoms, with careful monitoring of renal function to ensure that the kidney disease is not worsened. The role of interfe-

ron-based antiviral therapy for hepatitis C in persons with cryoglobulinemia is useful for those with mild to moderate kidney disease or after the acute flare has been controlled with immunosuppressive agents. Treatment leads commonly to disappearance of the crioglobulinemia.[42]

Membranoproliferative glomerulonephritis is another extrahepatic disorder associated to chronic HCV infection. Less often, HCV may cause focal segmental glomerulosclerosis or membranous or proliferative glomerulonephritis.[42] The former usually presents with proteinuria and hypocomplementemia. Although treatment is indicated in all of these cases, viral response is usually poor.[43,44]

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