

Approach to and management of patients with chronic hepatitis C virus infection and normal transaminase levels

Nelia Hernández Maldonado¹

Chronic infection with hepatitis C virus (HCV) is a dynamic disease from a biochemical perspective because transaminase levels fluctuate and may even fall within normal ranges at times. Although most patients with this disease have elevated alanine aminotransferase (ALT) levels, up to 46% of cases have persistently normal serum ALT levels despite the presence of HCV RNA.¹ Until recently, HCV patients with normal ALT levels were not considered for treatment because it was believed that this indicated that hepatic lesions were absent. The 1997 consensus conference² did not recommend HCV treatment for patients with normal transaminase levels. At the consensus conference of 2002,³ expert opinions regarding the site of the biopsy and the indications for treatment of patients with APN were divided. The following aspects of the management of APN patients are still the subject of debate.

For how long should potential APN patients be monitored and at what intervals should analyses be done to determine whether they have APN?

Most protocols define APN as at least three normal ALT values over a period of not less than 6 months.⁴ However, elevation of ALT levels may be delayed for 12 months in up to 21% of cases.⁵ The shorter the follow-up period, the greater the possibility of misdiagnosis of patients.

Are persistently normal ALT levels indicative of the absence of hepatic lesions?

Most histological studies in which the severity of lesions have been evaluated show that patients with APN have lower levels and activities of fibrosis than patients with elevated APN levels.^{6–10} However, significant fibrosis and even cirrhosis is present in 5%–19% of APN cases.^{1,5,6} These data show that liver damage cannot be presumed to be absent on the basis of a few ALT analyses.

What is the natural evolution of hepatitis C in APN patients?

Knowledge of the progression of fibrosis is fundamental for decisions about the evaluation and treatment of APN patients. Hui et al.¹¹ showed that patients with APN and an FO/F1 level of fibrosis at the time of the initial biopsy tended to develop less severe levels of fibrosis than patients with the same grade of fibrosis but elevated ALT levels. The difference between these groups was not significant when the initial level of fibrosis was more severe (F2). Puoti et al.¹² studied four couples of which one member had elevated ALT levels and the other had APN. Only patients with elevated ALT levels received treatment; the APN patients were denied treatment even if histological tests showed that they had hepatic lesions. A second biopsy 10 years after the first showed that the lesions had progressed from F0 to F3 and from F2 to F4 in the two untreated APN cases.

Are liver biopsies useful for initial evaluations? Is it important to take a biopsy sample prior to deciding on a treatment?

Liver biopsy constitutes a reference method for evaluation of the level of damage and fibrosis (staging) of liver disease. ALT levels are not correlated with histological findings.¹³ The usefulness of liver biopsies in patients with APN is controversial.¹⁴ The consensus conferences of 1997 and 1999 of the NIH and EASL, respectively, do not recommend biopsies for this group of patients, nor do they recommend treatment.^{2,4} In the consensus of the NIH of 2002,³ it was stated that larger studies on the usefulness of biopsies for this group of patients were required and that only those patients with favorable predictors of response to treatment, i.e., patients with HCV genotypes 2 or 3, should be treated. The most recent recommendations of the AASLD (The American Association for the Study of Liver Diseases) stated that liver biopsy is unnecessary, irrespective of ALT values.¹⁵ This recommendation and the absence of any clear ruling on the topic indicate that each case should be evaluated on an individual basis, taking many other factors into account.

¹ Clínica de Gastroenterología del Hospital de Clínicas de Montevideo, Uruguay.

Address for correspondence:
E-mail: nelia@adinet.com.uy

Does the response to treatment differ between APN patients and those with elevated ALT levels?

Although numbers of APN patients in studies of responses to treatment with interferon alfa plus ribavirin are low, they indicate that response rates of APN patients are similar to those of patients with elevated ALT levels.¹⁶⁻²⁰ In the first multicenter study to evaluate the efficacy and safety of peginterferon plus ribavirin, 491 patients with APN were studied 18 months before acceptance. The patients were randomized into three groups: 24 weeks of treatment, 48 weeks of treatment, and no treatment. The average SVR was 30% and 52% in patients treated for 24 and 48 weeks, respectively. In patients with HCV genotype 1, SVR after 48 weeks of treatment was 40%; in patients with HCV genotypes 2 or 3, SVR was 72% and 78% after 24 and 48 weeks of treatment, respectively.²¹

Should the decision to treat patients be based on biochemical (ALT), histological (fibrosis) or genomic (PCR) criteria?

The decision to treat patients should be based on all these criteria and also on aspects such as the age of patient, his/her motivation, the virus genotype, and the presence of comorbidities that constitute contraindications or major risks. Alberti et al.²² proposed an algorithm for treatment in which young individuals who are infected with genotypes 2 or 3 and are highly motivated and free of contraindications may receive treatment without the need for a biopsy. In patients older than 50 years with HCV genotypes 1 or 4 and co-morbidities, pre-treatment biopsies may constitute the decisive factors.

Recommendations of the consensus panel

Should patients with normal transaminase levels be excluded from treatment?

Patients with normal transaminase levels should be treated for as long as possible because several studies have shown that the risk-benefit ratio is justified. Although the panel did not reach consensus on whether it is necessary to take liver biopsies from this group of patients, most thought that this decision should be made on an individual basis.

Evidence quality: 3

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