



## Usefulness of liver biopsies in chronic infection with hepatitis C virus

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Although the liver biopsy alone is of little use for diagnosis of chronic hepatitis C, it is the most precise method for estimating the activity and stage of this disease. Liver biopsies can also provide information that is useful for assessing responses to treatments,<sup>1,3</sup> making prognoses,<sup>4</sup> detecting lesions, and in some cases, defining the urgency of treatment.

Recently, attempts have been made to substitute liver biopsies with noninvasive, low-cost, reproducible, accessible methods for the evaluation of chronic hepatitis C fibrosis. The arguments against biopsies concern the possibility of complications and the high cost of the procedure. At present, none of the noninvasive methods provides an accurate estimate of the intensity of fibrosis.<sup>5</sup> Moreover, several studies have shown that there is no correlation between clinical findings or aminotransferase levels and liver histology in cases of chronic hepatitis.<sup>8</sup> Thus, we conclude that the liver biopsy is still the ideal diagnostic standard.

Percutaneous liver biopsy, with or without guidance with ultrasound or computer-assisted tomography, is fast, safe, and the most common type of liver biopsy.<sup>9</sup> Menghini and Tru-cut needles are used most commonly. The advantages of the Menghini needle are its low caliber and the short time taken to obtain the biopsy sample, which reduce the number of complications. The main disadvantages of this method are fragmentation of the liver sample because of its small diameter and, in cases of cirrhosis, parenchyma samples without collagen bands around the regeneration nodules. The latter disadvantage is common to all suction needles and makes the diagnosis of cirrhosis difficult. The advantages of the Tru-cut needle are its greater diameter, less frequent fragmentation of the sample, and the ability to obtain liver parenchyma and fibrous tissue in cases of cirrhosis. The main disadvantage of the Tru-cut needle relative to the Menghini needle is that it has a higher frequency of complications.<sup>10</sup>

Colloreto et al.<sup>11</sup> carried out a study to determine the minimum size of puncture biopsy for evaluation of the

grades and stages of chronic hepatitis B and C. They recommended that the sample should be 22 mm long and 1.4 mm in diameter and should not contain less than 11 full portal spaces. When the number of portal spaces is less than 11, the activity and level of fibrosis is underestimated. In a similar study of virtual biopsies made using images of liver fragments obtained from hepatectomies, Bedossa et al.<sup>12</sup> reported that in biopsies  $\geq 25$  mm long, fibrosis was correctly diagnosed in 75% of cases of chronic hepatitis C; in biopsies 15 mm long, the corresponding figure was 65%. Biopsies obtained with needles less than 1 mm in diameter are of little use because middle fibrosis and cirrhosis are not detected in more than 60% of cases.<sup>13</sup>

In order to assess the extent of liver fibrosis from biopsy samples, the amount of type I collagen should be quantified using Masson's trichromic stain or sirius red, or the amount of elastic fibers should be quantified.

Numerical indexes should be used for evaluation of grades and stages of fibrosis in research studies and assays of therapeutic protocols. Such indexes are less subjective than histological descriptions and are suitable for statistical analysis of groups of patients. The ideal numerical system should be simple, easy to apply, include precise definitions of the variables of interest, and must have been validated. The most frequently used indexes are those of Knodell, Ishak, and the Metavir group.<sup>14</sup> The system of choice is a matter of personal preference. These systems are not quantitative measurements of fibrosis but consist of categories that afford an approximate idea of the intensity of lesions. Interobserver consistency is better when biopsies are evaluated by two pathologists and when evaluations are conducted by experts.<sup>15</sup>

The practice of taking routine liver biopsies from patients with chronic hepatitis C is debatable. In the opinion of some authors, biopsies are necessary to assess the intensity of inflammation and the grade of fibrosis; others consider that biopsies should be conducted selectively. In a multicenter study,<sup>16</sup> a group of experts was asked to predict the results of liver biopsies from the corresponding clinical and laboratory data of 81 patients with hepatitis C. Predicted activity and fibrosis were consistent with histological alterations in 55% and 56% of cases, respectively. The diagnosis of advanced fibrosis had a sensitivity of 53% and specificity of 56%. The authors concluded that liver biopsies are essential for the assessment of patients

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with chronic hepatitis C. One shortcoming of this trial is that in a few cases, an ultrasound was made and nonendoscopic study of esophagus to search the presence of advanced liver lesion. Andrinulli et al.<sup>17</sup> compared the effects of treatment of 78 patients who underwent biopsies with those of an equal number of patients who were not subjected to biopsies. The cases were matched by sex, age, and viral genotype; the patients with infection by B virus, previous treatment, decompensated cirrhosis and valuation for transplant. Viral clearances at three months, viral responses at the end of treatment, and SVRs of the two groups were similar. The authors concluded that biopsies should be restricted to patients with high probability of a lack of response to treatment.

The decision to conduct a biopsy depends on several factors: age of patient, viral genotype, aminotransferase level, presence of advanced liver injury or decompensated cirrhosis, and the coexistence of other diseases or liver lesions. The following protocol is proposed for determining whether liver biopsies should be conducted in patients with chronic hepatitis C infections:

1. Liver biopsy is recommended for:
  - a) patients infected with viral genotypes other than genotypes 2 or 3 who have elevated aminotransferase levels but no evidence of advanced liver disease (endoscopic detection of esophageal varices or ultrasonic detection of two or more of the following: spleen higher than 120 mm diameter of the hepatic portal vein greater than 12 mm, irregular liver margins, caudate lobe hypertrophy);
  - b) patients infected with any viral genotype who have normal aminotransferase levels (four determinations in 12 months) or elevated aminotransferase levels, a history of alcoholism, obesity, human immunodeficiency virus infection or any other disease that affects the liver; and
  - c) patients with normal aminotransferase levels for whom the urgency of treatment must be defined.
2. Liver biopsy is not considered necessary for patients:
  - a) infected with viral genotypes 2 or 3;
  - b) infected with any genotype and with a history of advanced liver disease; or
  - c) infected with any genotype and asymptomatic, older than 65 years, and with normal or elevated aminotransferase levels.
3. Liver biopsy is contraindicated in patients:
  - a) in whom treatment is contraindicated, or
  - b) who reject treatment.
4. A follow-up biopsy should be taken from patients who are coinfecting with hepatitis C virus and human immunodeficiency virus and present with progression of cirrhosis or worsening liver disease.

## Recommendations of the panel on the usefulness of liver biopsies

Liver biopsy is an important technique for histological assessment of the level of liver damage. The minimum criteria for assessment of the extent of liver fibrosis from biopsy samples are staining with hematoxylin/eosin and a dye specific for collagen.

Liver biopsies are recommended for patients who have chronic infection with genotype 1 hepatitis C virus. Post-treatment biopsies should not be restricted to research protocols. In hospital environments, posttreatment biopsies should preferably be performed under ultrasound guidance by health professionals with expertise in this technique.

There are no studies that compare the frequency of complications and the usefulness of samples for biopsies taken with or without ultrasound guidance. Ultrasound is useful for detecting focal lesions. Ultrasound guidance of the biopsy needle reduces the number of attempts needed to obtain a satisfactory sample, which in turn reduces morbidity<sup>19</sup> (opinion of experts).

The most commonly used numerical grading systems for evaluating the intensity of necroinflammatory lesions and fibrosis of chronic hepatitis C are those of Knodell, Isaac, and the Metavir group.<sup>14</sup> As none of these systems is superior to the others, the method of choice depends on personal preference. The main justification for such assays is that they facilitate detailed analysis of the efficacy of therapeutic strategies. For evaluation of fibrosis, at least two dyes (hematoxylin-eosin and Masson's trichromic stain) must be used (opinion of experts).

The interobserver consistency of numerical grading is greater when the sample is graded by two experts<sup>18</sup> (the quality of evidence for this recommendation was given a rating of 1). In the event that there is only one observer, it is advisable to evaluate the interobserver consistency. When made by pathologists who are not proficient with the scoring system, such assessments are of little value because they have poor consistency with assessments made by experts<sup>15</sup> (the quality of evidence for this recommendation was given a rating of 1).

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