

Medical Writers' Circle

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the management
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The Role of Liver Biopsy In Chronic Hepatitis C

The traditional gold standard to establish the diagnosis and stage chronic liver disease is liver biopsy. Historically, liver biopsy was the only diagnostic test available for the evaluation of liver disorders and was recommended in virtually all cases. However, chronic liver disease can now be accurately diagnosed, in the majority of cases, by the use of contemporary blood tests for acute and chronic hepatitis, autoimmune liver diseases, and hereditary liver diseases, or a careful history of medication use for drug-induced liver disease, alcohol abuse for alcoholic liver disease, and presence of risk factors (obesity, diabetes mellitus, hyperlipidemia) for nonalcoholic fatty liver disease. In some cases of liver disorders, such as hepatic granulomas and liver abnormalities occurring after liver transplantation, liver biopsy is required for precise diagnosis.

Expert consensus groups from the United States and Europe have recommended the routine performance of liver biopsy prior to initiation of antiviral therapy for chronic hepatitis C (1,2). These recommendations were developed during the era of interferon monotherapy, when the sustained virological response rate (SVR) for patients with genotype 1 was less than 10% and for genotypes 2 and 3 was 15% to 30%. The rationale for a pretreatment liver biopsy at the time of these

consensus conferences was to distinguish patients who might potentially benefit from interferon monotherapy, i.e., patients with significant fibrosis (stage 2 – portal fibrosis, stage 3 – bridging fibrosis, and stage 4 – cirrhosis) from those less likely to benefit from therapy (stage 0 – no fibrosis or stage 1 – portal fibrosis). These recommendations led to the routine performance of liver biopsy in nearly all patients who were newly diagnosed with chronic hepatitis C and potential candidates for antiviral therapy.

Recent studies have both supported and questioned the role of liver biopsy in patients with known clinical diagnoses, such as chronic hepatitis C virus (HCV) infection based on positive serological and virological blood tests. In an Italian study, Andriulli et al (3) studied 535 patients with chronic viral hepatitis who had undergone liver biopsy. Additional diagnoses were uncovered in only 4% of cases. Knowledge of the grade and stage of chronic hepatitis were considered of value by the treating physician in approximately 60% of cases, but antiviral treatment was not changed in 81% of cases. These investigators concluded that liver biopsy is less helpful than conventionally understood, because it generally neither increases the accuracy of clinical diagnosis nor affects the choice of therapy. On the other hand, Saadeh et al (4) agreed that liver biopsy did not yield new diagnoses

in patients with chronic hepatitis C, but concluded that biopsy provided useful information regarding staging, prognosis, and decisions regarding treatment.

Some of the traditional arguments in favor of routine liver biopsy in patients with chronic HCV infection can be questioned (5). Firstly, biopsy is proposed to be important to reveal an unsuspected secondary liver diagnosis, but the studies noted above did not support this argument. Secondly, liver biopsy is recommended to diagnose unsuspected cirrhosis, which may change the prognosis and considerations regarding therapy or follow-up (e.g., screening for hepatocellular carcinoma with regular alpha-fetoprotein and ultrasound). However, the finding of cirrhosis did not influence the decision for treatment in the study of Andriulli et al (3), as all patients were treated with antiviral therapy. In addition, noninvasive testing with imaging studies showing an irregular surface of the liver and/or an enlarged spleen and blood tests showing a low platelet count can often identify patients with advanced stages of fibrosis, i.e., bridging stage 3 fibrosis or cirrhosis. Thirdly, and most convincing, is the performance of liver biopsy to establish the grade and stage of chronic hepatitis C. However, cost-effective analyzes and patient preferences, with the recent improvements in the SVR after antiviral therapy for chronic hepatitis C, may be more dominant influences

in decisions regarding antiviral therapy than findings on biopsy.

Patients with chronic hepatitis C are often anxious regarding undergoing a liver biopsy, and many would prefer to avoid a biopsy. Patients frequently have anticipatory anxiety, which would be expected of a procedure that is associated with pain in 30%, severe complications in 3 per 1000, and death in 3 per 10,000 of patients (6). Some patients prefer to defer rather than undergo current therapy if they have no or minimal fibrosis because of side effects,

which genotypes 2 or 3, low viral load (< 2 million IU/mL), and early stages of fibrosis (stages 0 to 2) on liver biopsy are the most important. These factors can be used to predict a relatively better or worse than average chance of achieving a SVR. There are also evolving studies showing that early virological responses at different time points after beginning therapy, e.g., 12 weeks, are additional factors that may predict the likelihood of a SVR. In the study of Fried et al (8), a 2 log₁₀ drop or negative HCV RNA occurred at 12

tolerance to treatment with either systemic and psychiatric side effects or bone marrow depression. The presence of advanced fibrosis might influence the decision to continue therapy and use adjunctive therapies such as antidepressant drugs for serious psychiatric side effects or G-CSF for leukopenia or epoetin for anemia.

In conclusion, all patients with chronic hepatitis C who are candidates for antiviral therapy may not need to undergo a procedure for which there is much apprehension, a finite complication

blood tests that are markers of hepatic fibrosis or various formulae based on miscellaneous clinical and laboratory tests, to predict the stage of fibrosis without liver biopsy are needed. In addition, pretreatment and early treatment predictors with a high positive predictive value of a SVR also require further refinement to allow selection of patients with a high likelihood of success with antiviral therapy irrespective of liver biopsy findings.

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but are agreeable to therapy if they have advanced fibrosis – in this case a liver biopsy is necessary. As the outcomes of therapy have improved with the advent of combination treatment with interferon and ribavirin in 1998 and now peginterferon and ribavirin in 2001 (SVR of ~45% for genotype 1 and ~80% for genotypes 2 and 3) (7,8), more patients prefer empiric therapy in an attempt to achieve a SVR irrespective of whatever liver biopsy might show. Finally, some patients not only opt for therapy but also want to know their degree of hepatic fibrosis as a general indicator of prognosis. Thus, clinicians may not need to routinely perform routine liver biopsies in all patients with chronic hepatitis C and might consider using biopsy selectively, rather than routinely, to assist in decisions regarding therapy taking into account patient preferences after full education regarding the options (5).

There are a number of pretreatment factors that predict the success of antiviral therapy, of

weeks in 86% of patients treated with peginterferon alfa-2a and ribavirin, and 65% of these patients had a SVR. Thus, patients who have favorable pretreatment predictors noted above, especially genotypes 2 or 3 with an approximate 80% chance of a SVR, and are motivated to eradicate HCV might reasonably forgo a liver biopsy. Those who have unfavorable pretreatment predictors of success of therapy, such as genotype 1 and a high viral load, might be the best candidates for liver biopsy to influence the decision of whether or not to initiate therapy. Once therapy is initiated in patients not having a pretreatment liver biopsy, it is also possible to obtain a later liver biopsy during therapy, e.g., in patients not meeting early predictors of a SVR after 12 weeks of therapy. Patients found to have advanced fibrosis may warrant continuation of therapy even though the chance of success is relatively low. A biopsy might also be used after therapy is initiated if there is poor

rate, and personal and societal costs. Some clinicians are moving to selective rather than routine use of liver biopsy in patients with chronic HCV infection, reserving biopsy for circumstances in which biopsy would influence the decision regarding either initiation or continuation of therapy. It is of paramount importance that liver biopsy should not be a barrier to therapy; patients not desiring a biopsy should not be denied therapy. It is also important to make a distinction between physicians in private practice seeking a practical approach to the management of chronic hepatitis C versus investigators at tertiary centers, who are enrolling patients in pharmaceutically funded clinical trials or prospectively collecting liver biopsy data for their own research. Physician investigators are the usual educators across the country and generally have a bias in favor of routine liver biopsy based on the importance of liver biopsy in research studies. Better noninvasive markers, either newer