

The Role of Liver Biopsy in Chronic Hepatitis C

Jules L. Dienstag

The report of the 1997 National Institutes of Health Consensus Development Conference on hepatitis C endorsed pretreatment liver biopsy. We revisit the following questions: Does liver histology help determine the urgency of, and predict the likelihood of response to, antiviral therapy, and can surrogate markers supplant histological assessment? Because the rate of progression of chronic hepatitis C is influenced by baseline histological grade/stage, patients can be stratified into those with moderate to severe hepatitis, who merit imminent therapy, and those with mild hepatitis, in whom therapy can be postponed until more effective/tolerable treatments become available. Less advanced baseline histology has been shown to be an independent predictor of responsiveness to antiviral therapy. Although the predictive value of biopsy is insufficient to withhold therapy from patients with advanced fibrosis, baseline biopsy helps gauge expectations for the outcome of therapy. Reports have been published recently suggesting that laboratory markers can predict distinctions between low-grade fibrosis and therapy-indicating septal fibrosis/cirrhosis. These indices, however, are insufficiently reliable to predict histological distinctions in populations with varying prevalences of fibrosis/cirrhosis or to provide anything more than broad qualitative distinctions, far short of the potential information in a liver biopsy. For most patients, the value of pretreatment liver biopsy outweighs its risks, provides information about the urgency of treatment, and should be retained. Studies to identify noninvasive laboratory markers of histological activity and stage, especially genetic predictors of accelerated disease progression, command a high priority. (HEPATOLOGY 2002;36:S152-S160.)

As the efficacy of therapy for chronic hepatitis C improves, as acceptance of such therapy becomes more widespread, and as management of chronic hepatitis C extends from specialist hepatologists to non-specialists, the role of liver biopsy in the management of chronic hepatitis C is being re-examined. When the role of liver biopsy was considered during the previous Na-

tional Institutes of Health Consensus Development Conference in 1997, pretreatment liver biopsy was endorsed as the "gold standard" for assessing the grade of liver injury and stage of liver fibrosis in anticipation of antiviral therapy.^{1,2} The same recommendations appear in the consensus statement of the European Association for the Study of Liver Disease³ and the British Society of Gastroenterology⁴; are supported by the Centers for Disease Control, United States Public Health Service⁵; and are implied in the consensus statement on prevention and management of hepatitis C in the Asia-Pacific region.⁶ Since the 1997 National Institutes of Health Consensus Conference, a series of reports have appeared either supporting or challenging the role of such histological assessment in the management of chronic hepatitis C. In re-evaluating the value of liver biopsy, we should consider whether hepatic histology (1) provides prognostic information about the future natural history of chronic hepatitis C, (2) predicts the likelihood of response to antiviral therapy, and (3) remains the gold standard that it represented or can be supplanted by "surrogate" indicators.

Selecting patients for treatment would be easier if available therapy were uncomplicated, highly effective, simple to administer, limited in duration, and well tolerated. In patients with chronic hepatitis C, however, available ther-

Abbreviations: HAI, histology activity index; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

From the Gastrointestinal Unit (Medical Services), Massachusetts General Hospital, Boston; and the Department of Medicine, Harvard Medical School, Boston, MA.

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Address reprint requests to: Jules L. Dienstag, M.D., Gastrointestinal Unit (Jackson 7), Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114. E-mail, JDienstag@Partners.org; fax: 617-726-3763.

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Table 1. Scoring of Hepatic Fibrosis

Fibrosis	Knodell et al., HAI ¹⁰	Badossa et al., Metavir ⁷	Ishak et al., HAI ¹¹
None	0	0	0
Portal fibrosis (some)	1	1	1
Portal fibrosis (most)	1	1	2
Bridging fibrosis (few)	3	2	3
Bridging fibrosis (many)	3	3	4
Incomplete cirrhosis	4	4	5
Cirrhosis	4	4	6

apy is far from ideal, and many factors color the decisions of individual patients and their physicians. Antiviral therapy for chronic hepatitis C requires injection therapy; side effects are common and especially difficult to accept in a population of predominantly asymptomatic persons; approximately half of treated patients fail to respond to the best therapy available; for many patients progression is so slow and limited that the decision to treat is readily postponed; and, if the steady progress in efficacy of antiviral therapy over the last decade is an indication of progress to come, many patients might fare just as well to wait until antiviral therapy improves. Perhaps, for certain subgroups of patients (*e.g.*, those with HCV genotypes 2 and 3) response to therapy is so likely that the threshold for treatment is achieved in almost all cases; however, because most patients have genotype 1, and because 60% of patients in this category fail to respond, pretreatment variables that shed light on prognosis and likelihood of response to therapy are valuable for decision making about therapy.

Sampling error notwithstanding, if tissue obtained at biopsy is sufficient in size, interobserver agreement is very good, especially for fibrosis.^{7,8} To help standardize assessment of histology among pathologists, and especially to enhance objectivity of histological measurements among different investigators engaged in different clinical trials, several groups have proposed histological schemes for grading activity and staging fibrosis.⁹ Among these, the Histology Activity Index (HAI) of Knodell et al.¹⁰ and its modification by Ishak et al.¹¹ and the Metavir system⁷ are used most widely. In the HAI systems, necroinflammatory activity is graded on a scale of 0 to 18, while in the Metavir system, necroinflammatory activity is graded on a scale of 0 to 3. For quantifying fibrosis, which is more relevant to issues of pretreatment assessment of disease stage, the HAI, modified HAI, and Metavir systems rely on scales of 0 to 4 or 0 to 6 (Table 1).^{7,10,11}

From the perspective of the hepatologist, liver biopsy in patients with chronic hepatitis C is considered useful to suggest prognosis for progression; to help in determining the urgency of therapy; to exclude other forms of liver

disease; to predict responsiveness to antiviral therapy; and to provide baseline histology against which to compare future biopsies as histological progression or improvement is factored into later management decisions.² For all but the latter consideration, data have appeared supporting the role of liver biopsy.

On the other side of the balance sheet are the potential downsides of liver biopsy. Percutaneous liver biopsy is an invasive procedure that may meet with patient reluctance. Adverse events are a possibility. Data from large biopsy experiences suggest that transient pain occurs in approximately 30%, severe complications in 3%, and death in 0.03%.^{2,12,13} In the most recent assessment, the French Association for the Study of the Liver described complications after 2,084 liver biopsies during the calendar year of 1997.¹⁴ Moderate pain occurred in 20%, severe pain requiring intravenous analgesia or narcotics in 3%, vasovagal episodes occurred in 2%, severe complications in 0.57% (1 episode each of hemoperitoneum and pneumothorax and 3 episodes each of bile peritonitis and punctured viscera). No deaths were recorded. In addition, the need for a pretreatment liver biopsy may serve as a barrier to therapy, and the procedure is expensive, accounting for direct costs of \$1,500 to \$2,000 and for such indirect costs as time away from work and lost productivity.

The Role of Liver Biopsy in Assessing the Urgency of Antiviral Therapy (Prognostic Value of Liver Biopsy)

Although much is known about the natural history of chronic hepatitis C in large cohorts of affected persons, predicting the future course of the disease in any individual is difficult. Of the several potential prognostic variables, the most reliable appears to be histological grade and stage, as assessed by one of the several extant histological classification systems cited previously. Studies relying on serial liver biopsies suggest that patients with mild hepatitis and limited fibrosis progress slowly or not at all over a 10- to 20-year period, while those with moderate and severe inflammation (grade) and fibrosis (stage) progress inevitably to cirrhosis over a 20- and 10-year period, respectively.¹⁵ Similar observations have been reported by others.^{16,17} Therefore, a baseline biopsy is considered useful for determining the urgency of initiating therapy. Moreover, almost all instances of hepatitis C currently being discovered in clinical practice represent hepatitis C virus (HCV) infections acquired 1 to 3 decades earlier, originating at a time of life when "risky" behavior occurred, even transiently. Thus, for most patients undergoing liver biopsy for chronic hepatitis C, a current biopsy includes an approximate assessment of the impact on inflammation and fibrosis of several decades of HCV infec-

tion and virus-associated liver injury. These observations have been invoked as the primary justification for recommending liver biopsy before embarking on a course of antiviral therapy.

Based on such histological prognostication, many clinicians decline to pursue therapy in patients with mild chronic hepatitis C. Thus, this approach of distinguishing between mild, nonprogressive, and moderate-severe, progressive hepatitis requires a baseline liver biopsy. If, on the other hand, even patients with mild hepatitis were candidates for therapy, establishing this baseline histological distinction would be less important. In fact, Wong et al.¹³ suggested that treatment of mild chronic hepatitis with combination interferon/ribavirin is actually cost-effective, reduces the risk of cirrhosis, and prolongs survival. The comparison strategies for this analysis were watchful waiting without therapy versus liver biopsy repeated every 3 years and therapy introduced for histological progression in general versus liver biopsy repeated every 3 years and therapy introduced for histological progression to cirrhosis. In this analysis, the calculated costs of therapy involved the combination of standard interferon with ribavirin. Although sensitivity analyses were included to address uncertainties in the many estimates required for such an analysis, this analysis was based on costs of a previous generation of therapy, not the increased costs (or, on the other side of the coin, efficacy) of contemporary therapy with pegylated interferon and ribavirin. In addition, the analysis could not include the impact of the inevitable introduction of more effective, better-tolerated treatments that would justify postponing treatment for several years.

Although the 1997 Consensus Development Conference statement included a suggestion for follow-up biopsies in those felt to have limited histological grade and stage,¹ the value of this approach has not been subjected to scrutiny. Conceivably, a strategy could be envisioned in which therapy that is highly effective and better tolerated would be introduced in the future without another biopsy. In the absence of a subsequent biopsy the cost-effectiveness of treating mild hepatitis C would be marginal or negligible. Whether critiques of this approach of Wong et al.¹³ are substantial or quibbling, the perspective of individual patients and physicians may be very different and no less valid or compelling than the societal perspective adopted in that analysis. For many patients with mild disease and a likelihood of progression to cirrhosis that may be as low as 20% over 20 years, a viable strategy would allow postponing treatment for several years and embracing therapy without an additional liver biopsy when more highly effective treatments become

available. Indeed, in practice, routine treatment of mild chronic hepatitis C has not been widely embraced. Therefore, for many clinicians and their patients, baseline histology does help in determining the urgency of therapy.

Role of Liver Biopsy in Excluding Other Forms of Liver Disease

Liver biopsy is felt to be helpful in excluding other causes of liver injury that might confound interpretation of the clinical and histological expression of HCV infection. Because some patients with chronic hepatitis C have other, concomitant causes of liver injury, a pretreatment liver biopsy to exclude alternative factors such as fat, alcohol, or iron may shift clinical focus away from hepatitis C to the alternative process. As logical as excluding alternative diagnoses sounds, in practice, the yield of liver biopsy in identifying other liver disorders in cohorts of patients referred for management of hepatitis C is small. For example, in one retrospective analysis of 126 patients with hepatitis C evaluated at an urban teaching hospital, suspected other diseases were found in only 3 patients (2%), and unsuspected other disorders were identified in another 3 (2%).¹⁸ Thus, by the time a diagnosis of chronic hepatitis C is established clinically, especially among patient cohorts selected for referral, the likelihood that liver biopsy will unearth the presence of other liver disorders is low. On the other hand, however, some of the factors revealed by liver biopsy (*e.g.*, fat or iron) have been suggested to be cofactors in the progression of fibrosis^{19,20} and may be of benefit to the clinician in the global assessment of the patient. Such additional variables cannot be identified in the absence of histological assessment. Whether the value of such information can be shown in prospective studies to make a difference in outcome remains to be determined.

Role of Liver Biopsy in Providing Baseline Histology for Future Reference

As alluded to previously, another argument in favor of a pretreatment biopsy in patients with chronic hepatitis C can be made for anyone with any type of liver disorder for which treatment is an option. That is, a baseline biopsy obtained before committing a patient to long-term treatment preserves the value of potential subsequent histological assessment for management decisions made in the future. Subjecting this assumption to scrutiny in a prospective trial would be difficult to orchestrate; therefore, the likelihood is correspondingly low that objective data

Table 2. Absence of Bridging (Septal) Fibrosis/Cirrhosis as a Predictor of Nonresponse to Antiviral Therapy for Chronic Hepatitis C

Therapy	Histological Feature	Sustained Response	Sens	Spec	PVP	PVN	Accuracy
IFN monotherapy ²¹	Cirrhosis vs. noncirrhosis	10%	91%	27%	30%	90%	43%
		n = 125					
IFN and ribavirin ²²	Septal fibrosis vs. none	33%	86%	22%	46%	67%	50%
		n = 46					
PEG-IFN and ribavirin ²⁴	Bridging fibrosis vs. none	44%	76%	35%	57%	56%	57%
		n = 136					

Abbreviations: Sens, sensitivity; Spec, specificity; PVP, predictive value positive; PVN, predictive value negative; IFN, interferon; PEG-IFN, pegylated interferon.

to support this rationale for liver biopsy will ever be generated.

The Role of Liver Biopsy in Predicting Responsiveness to Antiviral Therapy

Although other predictors of responsiveness to therapy exist, the degree of fibrosis has also been shown to be an independent inverse predictor of response to therapy (Table 2). At the time of the 1997 Consensus Development Conference, Davis and Lau²¹ reviewed the literature and identified 7 clinical trials of interferon monotherapy for chronic hepatitis C involving 125 cirrhotic patients and 430 noncirrhotic patients. In this cohort, the absence of cirrhosis was a predictor of sustained responsiveness to 6 months of interferon monotherapy (standard therapy at the time), 30% for noncirrhotic patients versus only 10% for cirrhotic patients. The same association between absence of cirrhosis or absence of septal/bridging fibrosis and sustained responsiveness to antiviral therapy has been reported for cohorts of patients treated with standard interferon and ribavirin, 46% in the low-stage group versus 33% in the high-stage group²²; for patients treated with peginterferon monotherapy²³; and for patients treated with peginterferon and ribavirin, 57% in the low-fibrosis group versus 44% in the high-fibrosis group.²⁴ In multiple regression analyses, absence of bridging fibrosis/cirrhosis was an independent predictor of sustained responsiveness ($P \leq .01$); moreover, the predictive value of this histological variable was independent of duration of therapy,²² drug dose,²⁴ and even genotype.²²⁻²⁴

On the other hand, the negative predictive value of fibrosis or cirrhosis is too low to justify withholding therapy, and the need for therapy may be more compelling in this group of patients who have more advanced disease. Thus, although histology is an important variable to be taken into account in making treatment decisions, its accuracy in predicting responsiveness is too low to justify withholding therapy in compensated patients with advanced fibrosis or cirrhosis (Table 2).

Nonhistological Assessment of Histological Activity

Liver biopsy would be less important were other clinical or laboratory tests available that could reliably predict the grade of inflammatory injury or stage of fibrosis. Since the 1997 Consensus Development Conference, several investigators have focused on just such "surrogates" for histological findings. Because most patients referred for evaluation have moderate to severe chronic hepatitis on liver biopsy, and because liver biopsies have been found by some investigators to have a limited impact on decision making about treatment,^{25,26} the importance of a pre-treatment liver biopsy might be questioned.

Although necroinflammatory activity on biopsy has prognostic value in patients with chronic hepatitis C, most clinicians focus more on the stage of fibrosis in their decision making about antiviral therapy. Not surprisingly, then, most investigators searching for surrogate markers of histology have focused on distinguishing cirrhosis from noncirrhosis and, because moderate to severe fibrosis is often the histological variable on which treatment decisions are based, on distinguishing between septal/bridging fibrosis ($\text{HAI} \geq 3$ or Metavir stage $\geq \text{F2}$) and milder forms of fibrosis (absent of periportal) (Table 1). Elsewhere in this supplement, Fontana and Lok²⁷ have reviewed the current status in development of biochemical tests specific for fibrosis, such as procollagen peptides and hyaluronic acid. None of these can be relied on with confidence to establish histological stage. Many investigators, however, have attempted to identify either single or constellations of several common laboratory markers that distinguish between moderate fibrosis/cirrhosis and lesser grades of fibrosis. Although some of these constellations include one or more biochemical markers of fibrosis, most focus primarily on more routine clinical and laboratory features. Among these are clinical impression (predictions based on such features as spider angiomas, hepatic and splenic enlargement, white blood cell count, alanine ami-

Table 3. Distinguishing Between Cirrhosis and Absence of Cirrhosis Based on an AST/ALT Ratio Greater Than 1

Study	No. of Patients	Prevalence of				
		Cirrhosis	Sens	Spec	PVP	PVN
Reedy et al., 1998 ³³	77	30%	44%	94%	77%	78%
Sheth et al., 1998 ³⁴	139*	34%	53%	100%	100%	81%
Park et al., 2000 ³⁵	153	20%	47%	96%	74%	88%
Imperiale et al., 2000 ³⁶	177*	23%	56%	90%	64%	87%
Pohl et al., 2000 ³⁷	153	24%	47%	82%	43%	84%

Abbreviations: Sens, sensitivity; Spec, specificity; PVP, predictive value positive; PVN, predictive value negative.

*Included patients with decompensated cirrhosis and with concomitant alcoholism.

notransferase [ALT] levels, bilirubin, albumin, ferritin, and age)^{25,28}; platelet count²⁹; age-platelet index³⁰; aspartate aminotransferase (AST)^{31,32}; AST/ALT ratio alone³³⁻³⁷ or in combination with platelet count³⁷; 5- and 6-marker indices based on α_2 macroglobulin, haptoglobin, gamma glutamyl transpeptidase, γ globulin, bilirubin, and apolipoprotein A₁³⁸; AST, platelets, and albumin³⁹; discriminant score based on prothrombin time expressed as international normalized ratio, ALT/AST ratio, and platelet count^{18,40}; discriminant score based on fibronectin, ALT, prothrombin time, pseudocholinesterase, manganese superoxide dismutase, N-acetyl- β -galactosidase⁴¹; discriminant score based on γ globulin, hyaluronidate, platelet count, and gender⁴²; and discriminant score based on hyaluronic acid, procollagen III nucleoprotein, type IV collagen, α_2 macroglobulin, TIMP-1, YKL-40, laminin, and apolipoproteins A₁ and A₂.⁴³

Distinguishing Between Cirrhosis and Noncirrhosis. Based on the known increase in AST compared with ALT that occurs in cirrhotic patients with viral hepati-

ty,⁴⁴ several investigators attempted to distinguish cirrhotic from noncirrhotic patients with hepatitis C in retrospective analyses by identification of those with AST/ALT ratios exceeding 1 (Table 3).³³⁻³⁷ This approach was insensitive (high false-negative rate) and had a poor positive predictive value (high false alarm rate); in each case, the investigators reported that applying this test would have been inadequate for diagnostic purposes, requiring liver biopsy in a substantial proportion of cases to establish a diagnosis of cirrhosis. Other investigators applied other clinical and laboratory criteria retrospectively to distinguish between cirrhotic and noncirrhotic patients with hepatitis C (Table 4).^{18,25,28,29,41,42} Despite the fact that some of these approaches discriminated fairly well between cirrhosis and its absence, in most cases, such non-histological methods would have avoided biopsies in only a small minority of patients.¹⁸

Distinguishing Between Septal/Bridging Fibrosis and More Limited Fibrosis. The distinction between cirrhosis and its absence provides very little information about stages of fibrosis short of cirrhosis. Because baseline biopsies can provide information that clinicians can rely on to predict the future rate of progression to cirrhosis, and because the presence of septal/bridging fibrosis (HAI \geq 3; Metavir \geq F2) is felt by wide consensus to represent an indication for the institution of antiviral therapy, several investigators have focused on non-histological identification of bridging fibrosis (Table 5).^{30,37,38,40,43} Some of these approaches are more promising than others, but as a group, they suffer from low sensitivity, specificity, predictive value positive, or predictive value negative.

Two examples are illustrative. Pohl et al.³⁷ performed a retrospective analysis of biopsies from 211 patients with

Table 4. Distinguishing Between Cirrhosis and Absence of Cirrhosis Based on Clinical and Laboratory Features Other Than AST/ALT Ratio alone

Study	No. of Patients	Prevalence of Cirrhosis	Approach	Sens	Spec	PVP	PVN
Ikeda et al., 2000 ⁴²	205	18%	Discriminant function*	84%	93%	84%	93%
Romagnuolo et al., 2001 ²⁸	54	7%	Clinical prediction	94%	100%		
Renou et al., 2001 ²⁹	110†	13%	Low platelets			93%	99%
Fortunato et al., 2001 ⁴¹	103‡	48%	Discriminant function§			81% to 93%	90% to 94%
Saadeh et al., 2001 ¹⁸	126	29%	Discriminant score cirrhosis > 7 noncirrhosis \leq 3	15% 85%	100% 58%	100%	73%
Andriulli et al., 2001 ²⁵	535	11%	Clinical impression	93%	32%	89%	42%

NOTE. Test characteristics provided or calculated from data in article when available.

Abbreviations: Sens, sensitivity; Spec, specificity; PVP, predictive value positive; PVN, predictive value negative.

* γ globulin, hyaluronic acid, platelet count, and gender (this study was based on peritoneoscopy as well as liver biopsy).

†Included patients with concomitant alcoholism.

‡Included patients with decompensated cirrhosis.

§Fibronectin, pseudocholinesterase, ALT, manganese sulfoxide dismutase, n-acetyl- β -galactosidase; cutoff to identify cirrhosis was a score of < -0.22 .

||Included patients with concomitant alcoholism, hepatitis B, and hepatitis D.

Table 5. Distinguishing Between Low-Stage Fibrosis and Bridging/Septal Fibrosis Based on Clinical and Laboratory Features

Study	No. of Patients	Prevalence of Septal Fibrosis	Approach	Sens	Spec	PVP	PVN
Bonacini et al., 1997 ⁴⁰	194	60%	Discriminant score $\geq 8^*$	46%	98%	93%	77%
Poynard et al., 1997 ³⁰	500	69%	Age-platelet index score $\dagger \geq 6$	45%	96%	96%	42%
Pohl et al., 2001 ³⁷	153	24%	AST/ALT > 1 Platelets $< 150k$	41%	99%	93%	85%
MULTIVIRC et al., 2001 ³⁸	134	45%	6-marker index \ddagger ≥ 0.6 ≤ 0.1	70% 100%	95% 22%	91% 50%	76% 100%
Patel et al., 2002 ⁴³	194	60%	Discriminant Score \S	79%	68%	78%	68%

NOTE. Test characteristics provided or calculated from data in article, when available.

Abbreviations: Sens, sensitivity; Spec, specificity; PVP, predictive value positive; PVN, predictive value negative.

*Discriminant score 0 to 11 based on platelet count, AST/ALT ratio, and prothrombin time.

\dagger Index of 0 to 10, score ≥ 6 supports diagnosis of fibrosis F2-F4 (Metavir).

\ddagger Index based on α_2 macroglobulin, haptoglobin, gamma glutamyl transpeptidase, γ globulin, bilirubin, and apolipoprotein A₁; scale of 0 to 1.0.

\S Discriminant score based on 3 markers from among the following: hyaluronic acid, procollagen III nucleoprotein, type IV collagen, α_2 macroglobulin, TIMP-1, YKL-40, laminin, and apolipoproteins A₁ and A₂.

chronic hepatitis C seen in their center; 153 were nonalcoholic (24% had Metavir fibrosis scores of 3-4), and 58 had concomitant alcoholism. When patients with alcoholism and hepatitis C were evaluated together, no correlation was found between AST/ALT ratio and Metavir fibrosis stages 0-4. When the analysis was confined to patients with isolated chronic hepatitis C, those with fibrosis stages 0-2 were clearly distinguished from those with fibrosis stage 3-4 ($r = 0.297$; $P < .00$). Confining the analysis to those with hepatitis C alone, Pohl et al.³⁷ found a strong inverse relation between platelet count and fibrosis score ($r = 0.560$; $P < .00$). When AST/ALT greater than 1 was combined with platelet count, these investigators found the best test characteristics for a platelet count was a threshold less than 150,000 (as shown in Table 5); although the sensitivity of this combination of laboratory values was insensitive (41%), it was very specific (99%) and had a high positive predictive value (93%) and a fairly good negative predictive value (85%). Moreover, this approach relied on readily available laboratory tests. The authors concluded, however, that this approach was very inaccurate for patients with low fibrosis scores (0-1) and that a biopsy could have been avoided in only 7% of the cohort. If alcohol is a potential contributor, this index has no predictive value. Another limitation is the inability of this index to distinguish between stage 3 fibrosis and cirrhosis (stage 4). In addition, the threshold for introducing antiviral therapy is a Metavir fibrosis score of F2, not F3.

Poynard and colleagues^{30,38} of the MULTIVIRC group have been attempting to identify noninvasive markers of fibrosis for several years. More recently, they have focused on a 5- or 6-marker index, on a scale of 0 to 1.0, relying on a series of nonroutine markers, α_2 macroglobulin, haptoglobin, gamma glutamyl transpeptidase, γ

globulin, bilirubin, and apolipoprotein A₁. Either of these 2 indices (the 5-marker index or the 6-marker index) correlates very well with Metavir fibrosis stage, and the area under receiver-operating characteristic curves (sensitivity plotted against 1-specificity) is high, exceeding 0.8 (1.0 is a perfect test, and 0.5 is correct no more often than chance alone). With a 6-marker index of fibrosis, these investigators could distinguish between Metavir fibrosis stage 0-1 versus 2-4 (the threshold for introducing therapy) in a group of 134 patients with chronic hepatitis C (prevalence of F2-4 of 45%). Based on this pretest probability of 45%, they found that patients with an index ≥ 0.6 had a positive predictive value exceeding 90%, while those with an index of ≤ 0.1 had a negative predictive value of 100% (Table 5). Thus, if a patient with chronic hepatitis C has a high index (≥ 0.6), the test is very specific with a high positive predictive value; fibrosis stage 2-4 is very likely. If a patient with chronic hepatitis C has a low index (≤ 0.1), none will have fibrosis stage 2-4, i.e., everyone with such a low score can be predicted with confidence not to have moderate or severe fibrosis. Based on this calculation, they concluded that liver biopsy could have been avoided in 46% of their study cohort.

Reliance on such an index has its proponents, and some may rely on this approach to avoid liver biopsies in a proportion of cases. Reservations worth emphasizing, however, include the fact that the MULTIVIRC index³⁸ relies on non-routine laboratory tests and a cumbersome calculation (available on a dedicated website). This index does not distinguish among fibrosis stages F2, F3, and F4, each of which has different prognostic significance. Essentially, if this index is used to replace histology, an underlying assumption is that the only valuable information to be derived from a liver biopsy is the distinction between these 2 broad categories of fibrosis. Such indices are blunt

instruments that do not provide all the information potentially available from a liver biopsy. In fact, liver biopsies do not provide simple yes or no answers; instead, they provide a wealth of qualitative data that are not readily reduced to simplistic distinction. Finally, such indices are highly influenced by pretest probability and are not generalizable to different populations with different prevalences of fibrosis or cirrhosis. Most of these indices are derived from populations biased by their referral to clinical research centers, and the complex models may not be applicable to individual patients or physician practices. At low prevalences of fibrosis/cirrhosis, these tests are more accurate at excluding fibrosis/cirrhosis, while at high prevalences of fibrosis/cirrhosis, these tests are more accurate in establishing fibrosis/cirrhosis. How far can we generalize from a population with a prevalence of substantial fibrosis of 45%?

Similarly, Poynard and colleagues have proposed a related index, which combines both septal fibrosis (F2-F4) and moderate necroinflammatory activity (Metavir grade A2-A3), either of which is considered an indication for therapy. This fibrosis-activity index, based on 6 variables (α_2 macroglobulin, haptoglobin, gamma glutamyl transpeptidase, bilirubin, apolipoprotein A₁, and ALT), has been applied retrospectively to a cohort of 352 patients treated in a multicenter, international clinical trial of pegylated interferon alfa-2b and ribavirin (Poynard et al., personal communication, May 2002). Based on a sensitivity cutoff of 0.3 to identify a sufficient stage and grade to justify initiating therapy, this approach has a sensitivity of 90% and a positive predictive value of 88%, but a specificity of 36% and negative predictive value of 40%. For the corresponding specificity cutoff of 0.4 to identify patients with low stage/grade, the test has a specificity of 80% and predictive value negative of 90%, but a sensitivity of 55% and predictive value positive of 33%. In this population of patients, all of whom were referred to and treated in a clinical trial of antiviral therapy, application of this fibrosis-activity index would have identified 55 patients (16%) who might have been judged to have too limited injury and scarring to merit therapy. Certainly, the high pretest probability of treatment-meriting histology guaranteed a relatively high level of accuracy in establishing fibrosis, but these indices might not be applicable to a routine cross section of community-derived patients with chronic hepatitis C.

Thus, as far as investigators have progressed in arriving at surrogates for liver histology – and this progress over the last 5 years is impressive – neither a single test nor a combination of clinical and laboratory features has been shown to have sufficient predictive value for the presence/absence of fibrosis/cirrhosis and or moderate necroin-

flammatory activity. Similarly, baseline biopsies have been reported to show unexpectedly mild liver disease in some patients referred for treatment, including persons with hemophilia,⁴⁵ with injection drug use,⁴⁶ and women who received contaminated anti-D immune globulin in Ireland⁴⁷ and Germany.⁴⁸ In contrast, among patients referred for clinical trials of antiviral therapy, cirrhosis may be unexpectedly frequent, for example, occurring in half of the patients with well-compensated chronic hepatitis treated in the first randomized trial of interferon alfa.⁴⁹ Thus, to date, nonhistological assessments applied broadly beyond a limited, idealized study cohort lack the utility to supplant liver biopsy in the initial assessment of suitability for treatment.

Importance of Liver Biopsy in Special Patient Subgroups

Patients With Normal ALT Activity. Another area of potential controversy is the subset of patients with chronic hepatitis C but persistently normal aminotransferase activities. Anecdotal reports have appeared to show that some of these patients have histologically very severe or advanced liver disease,^{50,51} suggesting that all such patients require liver biopsy to unearth clinically subtle but advanced liver disease. When group data are evaluated, however, the preponderance of evidence suggests that severe liver injury is the marked exception in such patients.⁵²⁻⁵⁵ Moreover, among patients with chronic hepatitis C and *persistently* normal aminotransferase levels, histological activity, as monitored by sequential liver biopsies over more than half a decade, has been documented not to progress.⁵⁶⁻⁵⁹ Therefore, and because the last National Institutes of Health Consensus Development Conference in 1997 failed to identify any benefit of interferon monotherapy in this subgroup,¹ many authorities are reluctant to pursue liver biopsy in patients with normal aminotransferase activity. As new evidence begins to emerge, however, suggesting that combination antiviral therapy with interferon and ribavirin may be equally effective in patients with elevated and normal aminotransferase activities (as summarized elsewhere in this supplement), the role of liver biopsy in the subset of patients with normal aminotransferase levels will have to be re-examined. Despite improved efficacy of contemporary antiviral therapy in this group, with its associated promise of “cure,” the vast majority of these patients, as long as they maintain normal biochemical activity, are highly unlikely to progress histologically. If the pace of disease progression in this group is slow and the pace of new drug discovery rapid, many people with normal aminotransferase activity may do just as well to wait, without current

liver biopsy or therapy, until their disease becomes biochemically active or until more efficacious and better tolerated therapies are developed.

Patients With HCV Genotypes 2 and 3. As stated previously, an important premise is that antiviral therapy for chronic hepatitis C would be more widely, perhaps universally, embraced were it uncomplicated, highly effective, simple to administer, limited in duration, and well tolerated. In patients with HCV genotypes 2 and 3, the frequency of sustained responses to short-term (6 months) therapy is so high that many of these conditions are met. Under these circumstances, then, the argument could be made that the benefits of treatment outweigh its inconvenience and beg for early application, regardless of histological features. Based on these considerations, some authorities have concluded that the need for liver biopsy in this subgroup is less compelling. On the other hand, the value of baseline histology as a predictor of responsiveness is independent of genotype.²²⁻²⁴ Therefore, the same rationale for a baseline liver biopsy as a prelude to therapy in patients with chronic hepatitis C in general can be applied to patients with non-1 genotypes in particular.

Conclusions

In most patients with chronic hepatitis C, the value of pretreatment liver biopsy outweighs its risks. For contemporary antiviral therapy of chronic hepatitis C, pretreatment liver biopsy, which provides important information about prognosis and the urgency of treatment as well as about likelihood of response to therapy, should be retained. Although much progress has been made, surrogate laboratory markers cannot supplant histological assessment of hepatic necroinflammatory activity and fibrosis. The role of liver biopsy in patients with normal ALT activity and in patients with HCV genotypes 2 and 3 remains the subject of debate.

Future Research Needs

Future research should focus on delineating how broadly histological assessment should be implemented and whether other clinical features suffice to supplant liver biopsy under certain circumstances. Will the role of liver biopsy change in patients with normal aminotransferase levels if antiviral therapy is applied more broadly in this group? Will the contribution of liver biopsy change as the efficacy and tolerability of antiviral therapy improve? Because liver biopsy is invasive and resource-consuming, the search for noninvasive laboratory markers of necroinflammatory activity, fibrosis, and cirrhosis merits our attention and resources. Commanding an even higher priority should be the quest for genetic markers associated

with accelerated disease progression that may be better predictors of progression and response to therapy than histological features.

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