

Role of Liver Biopsy in Management of Chronic Hepatitis C: A Systematic Review

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This systematic review addresses 2 questions pertinent to the need for pretreatment liver biopsy in patients with chronic hepatitis C: how well do liver biopsy results predict treatment outcomes for chronic hepatitis C? How well do biochemical blood tests and serologic measures of fibrosis predict the biopsy findings in chronic hepatitis C? Medline and other electronic databases were searched from January 1985 to March 2002. Additional articles were sought in references of pertinent articles and recent journals and by querying experts. Articles were eligible for review if they reported original human data from a study that used virological, histological, pathologic, or clinical outcome measures. Paired reviewers assessed the quality of each eligible study and abstracted data. Studies suggested that advanced fibrosis or cirrhosis on initial liver biopsy is associated with a modestly decreased likelihood of a sustained virological response (SVR) to treatment. Also, studies relatively consistently showed that serum aminotransferases have modest value in predicting fibrosis on biopsy; that extracellular matrix tests hyaluronic acid and laminin may have value in predicting fibrosis, and that panels of tests may have the greatest value in predicting fibrosis or cirrhosis. Biochemical and serologic tests were best at predicting no or minimal fibrosis, or at predicting advanced fibrosis/cirrhosis, and were poor at predicting intermediate levels of fibrosis. Thus, evidence suggests that liver biopsy may have some usefulness in predicting efficacy of treatment in patients with chronic hepatitis C, and biochemical blood tests and serologic tests currently have only modest value in predicting fibrosis on liver biopsy. (HEPATOLOGY 2002;36:S161-S172.)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HAI, histology activity index; HCV, hepatitis C virus; P-III-P, procollagen type III peptidase; SVR, sustained virological response; TNF, tumor necrosis factor.

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For patients with chronic hepatitis C, the role of liver biopsy before treatment is somewhat unclear. Many experts recommend pretreatment liver biopsy to exclude other diseases and to determine the degree or stage of hepatic fibrosis.¹⁻⁴ However, the value of liver biopsy in predicting treatment response is incompletely defined, and liver biopsy can be associated with serious complications and significant expense. As a result, some experts have questioned the role of liver biopsy in management of hepatitis C^{3,5,6} and have sought to identify noninvasive tests that could replace a liver biopsy.

We conducted a systematic review of the literature on 2 key questions: (1) how well do the results of pretreatment liver biopsy predict outcomes of treatment in patients with chronic hepatitis C? and (2) how well do biochemical blood tests and serologic markers of fibrosis predict the degree of fibrosis on liver biopsy in patients with chronic hepatitis C?

Materials and Methods

Identification of Target Population and Specific Questions. We defined the target population as patients with chronic hepatitis C. We formulated the key ques-

tions after meeting with the Planning Committee that was responsible for the 2002 Consensus Development Conference on Management of Hepatitis C and then obtaining input from external experts. Details about the identification of questions are available in a separate report.⁷

Literature Search. We conducted a search of literature from January 1996 through March 2002 using DIALOG (Cary, NC), a commercial database vendor that has access to several electronic databases including MEDLINE. To minimize the chance of missing an important study, we also searched MEDLINE back to 1985, conducted a manual review of reference lists in key studies, and reviewed the table of contents of recent issues of journals most likely to publish relevant studies.

We included the search for studies on liver biopsy in our overall search for articles on key questions in the management of hepatitis C, as described in our comprehensive evidence report.⁷ The search strategy was designed by experts at the National Library of Medicine (Bethesda, MD) to maximize the likelihood of detecting all pertinent peer-reviewed studies. After developing a search strategy for MEDLINE, the search experts modified the strategy to fit the other electronic databases.

Abstract Review. Paired reviewers independently screened the article titles identified by the search and excluded those that did not meet our eligibility criteria. The exclusion criteria were: language other than English, no human data, no original data, no information relevant to management of hepatitis C, only basic science, did not apply to one of our questions, meeting abstract, and other incomplete reports.

The paired reviewers then independently reviewed the abstracts of the remaining citations. Abstracts were excluded if both reviewers agreed that they did not meet eligibility criteria. Disagreements between reviewers were adjudicated in person.

Article Review and Data Extraction. We used a standardized form for assessing study quality and forms for extracting information on the characteristics and results of each type of study. To focus the review on articles that were most likely to give useful data on the questions, we excluded studies that (1) were not designed to address one of the questions; (2) addressed management of hepatitis C in liver transplant patients only; or (3) had less than 30 study subjects. In our review of studies on the relation of pretreatment histology to outcomes of treatment, we included only randomized controlled trials, because they would provide the strongest evidence on whether pretreatment histological findings are independent predictors of the efficacy of one treatment strategy compared with another. We were particularly interested in deter-

mining whether there was an interaction between pretreatment histology and specific treatment regimens. While cohort studies could provide some evidence of the relation between pretreatment histology and the response to a given treatment regimen, they are susceptible to selection bias in that patients could be excluded from a cohort on the basis of pretreatment histological findings. This type of selection bias would make it difficult to determine whether the relative efficacy of different treatment regimens depends on histological findings. We also required at least 24 weeks of follow-up. We did not include studies that were included in the previous systematic reviews that we reviewed in our complete evidence report.⁷ For the question on tests to predict fibrosis, we included only studies that evaluated biochemical blood tests or serologic tests that could serve as measures of liver fibrosis.

The study quality assessment form included the following categories: representativeness of study population (5 items); bias and confounding (1 to 4 items); description of management or test (1 to 2 items); outcomes and follow-up (5 items); and statistical quality and interpretation (4 items). The items on this form were derived from forms used in previous systematic reviews⁸ and can be found in our complete evidence report.⁷ Not all items applied to both questions addressed in this review. Each applicable item could be assigned a score of zero (criteria not met), 1 (criteria partially met), or 2 (criteria fully met). The score for each category of study quality was the percentage of total points available in each category and could range from 0% to 100%. The overall quality score was the average of the 5 categorical scores.

The data extraction form included items that described the type of study, geographic location, definition of study groups, specific aims, eligibility criteria, test characteristics, characteristics of subjects, and results.

We reviewed each eligible article in pairs, including at least one reviewer with clinical training and one with training in epidemiology and research methods. One reviewer completed the quality assessment and data extraction forms, and the second reviewer checked the material abstracted; they resolved differences by consensus.

After entering the data into an Access (Microsoft, Seattle, WA) database, we created evidence tables to display the information across studies. These detailed evidence tables are in our comprehensive evidence report.⁷

Evidence Grades. We graded the strength of evidence using a scheme derived from previous Evidence Based Practice Center projects.^{8,9} Evidence Grade A (strong evidence) was given when appropriate data were available, including at least one well done study, the study population was sufficiently large, there was an adequate reference standard, data were consistent, and the test definitively

was or was not useful. Grade B (moderate evidence) was given when appropriate data were available, the study population was sufficiently large, there was an adequate reference standard, the data were reasonably consistent, and the data indicated the test was or was not likely to be useful, but insufficient evidence to conclude definitively. Grade C (weak evidence) was given when some data were available, the study population was reasonably large, and there was insufficient evidence to conclude that a test was or was not likely to be useful. Grade I (insufficient evidence) was given when appropriate data were not available or an insufficient number of patients were studied.

Five members of our team independently graded the strength of the evidence on each question. If they disagreed, the final grade was based on the opinion of the majority.

Peer Review Process. An external group of experts reviewed a draft report detailing the methods and results of our review. This group included experts in hematology and infectious diseases, experts in clinical epidemiology, representatives of selected professional organizations (e.g., the American Association for the Study of Liver Diseases, and the American College of Physicians–American Society of Internal Medicine), and representatives of governmental agencies (e.g., the National Institutes of Health).

Results

Results of Literature Search. As detailed in our complete Evidence Report,⁷ we found 21 studies that met eligibility criteria for key question 1 and 66 studies that met our eligibility criteria for key question 2.

Relation of Pretreatment Biopsy Findings to Treatment Outcomes

Characteristics of Studies. Most of the studies on question 1 were conducted in the United States or Europe. Almost all studies excluded patients with other forms of liver disease, including hepatitis B, and several excluded patients with decompensated liver disease. Most also excluded women who were pregnant or breast feeding, patients with active intravenous drug use, heavy alcohol use, anemia, human immunodeficiency virus (HIV) infection, or other significant comorbidity.

In all of the studies, the majority of participants were men with the mean age ranging between 34 and 59 years. The mean serum alanine aminotransferase (ALT) value was between 65 and 200 mg/dL with the duration of infection ranging from 5.5 to nearly 20 years. The distribution of the initial biopsy findings varied, and many

studies used different reporting methods. However, both cirrhotic patients and non-cirrhotic patients were included in all groups. Hepatitis C virus (HCV) genotypes varied according to the countries in which the studies were performed.

Quality of Studies. The median overall quality score for the eligible studies was 64% with a range of 31% to 75%. Most studies had a representativeness score, outcomes assessment score, and statistical analysis score \geq 75%. Although these randomized, controlled trials generally used appropriate methods for measuring outcomes, very few reported on the incidence of complications from the biopsy. Also, the bias and description scores tended to be lower than the scores in the other categories. For question 1, the assessment of potential bias and confounding was based on whether the study performed an independent and blind comparison of the outcomes to the biopsy results. The description score for question 1 was based on the adequacy of the study's description of the technique and size of the biopsy.

Results of Multivariate Analyses. Twelve studies presented multivariate analysis with pretreatment histological results considered as an independent variable in predicting virological or histological outcomes¹⁰⁻²¹ (Table 1). In the study with peginterferon and ribavirin, the absence of cirrhosis was associated with an increased rate of sustained virological response (SVR) to therapy in both univariate and multivariate analyses.¹⁰ In one of the studies of standard interferon and ribavirin, the multivariate analysis did not show a significant association between SVR and initial histological grade (amount of inflammation), initial histological fibrosis stage (amount of fibrosis), or initial presence or absence of cirrhosis.¹⁴ In another study with standard interferon alfa-2b and ribavirin, multivariate analysis reported a significant association between pretreatment fibrosis and virological nonresponse to treatment, but the details regarding the magnitude and significance of this relationship were not provided.¹³ The third study with standard interferon and ribavirin found no significant association between pretreatment grade and ultimate response to therapy in multivariate analysis.¹² This study did demonstrate a significant association between pretreatment fibrosis and virological response in univariate analysis. In the study evaluating peginterferon versus standard interferon alfa-2b, baseline liver histology was not associated with SVR, although the histological response rates were higher than the virological response rates.¹⁵ In contrast, in the study with peginterferon compared with interferon alfa-2a, virological response was associated with the absence of cirrhosis or fibrosis.¹⁶

In one study evaluating different doses of interferon, the pretreatment histology activity index (HAI) was a sig-

Table 1. Results of Multivariate Analyses of Relation Between Pretreatment Histology and Outcomes of Treatment for Chronic Hepatitis C

Author, Year	N	Treatment Groups	Outcome	Histological Variable(s)	Adjusted Parameter Estimate Relating Histology to Outcome	Adjusted P Value
Manns, 2001 ¹⁰	1,530	PEG/RBV vs. IFN/RBV	SVR	Absence of cirrhosis	NR	NR
				Absence of bridging fibrosis or cirrhosis	NR	<.01
Berg, 2000 ¹¹	185	IFN + RBV vs. IFN	SVR	Histologic activity, grade, and stage	NR	NR
Mangia, 2001 ¹²	192	IFN + RBV vs. IFN	SVR	Histologic grade	NR	NS
				Histologic stage	NR	NS
McHutchison, 2000 ¹³	1,712	IFN + RBV vs. IFN	SVR	Degree of fibrosis	NR	NR*
Saracco, 2001 ¹⁴	594	IFN + RBV vs. IFN	SVR	Grade \geq 5.2	Odds ratio: 1.0	.8
				Stage \geq 2.3	Odds ratio: 0.93	.8
				Cirrhosis	Odds ratio: 0.5	.2
Lindsay, 2001 ¹⁵	1,299	PEG vs. IFN	SVR	HAI score	NR	NS
Zeuzem, 2000 ¹⁶	531	PEG vs. IFN	SVR	Absence of cirrhosis or bridging fibrosis	Odds ratio 2.2	.03
Ascione, 1998 ¹⁷	80	Different doses of IFN	SBR	Chronic hepatitis vs. cirrhosis	NR	NS
Kumada, 1996 ¹⁸	54	Different doses of IFN	SVR	HAI score	0.0018†	.98
Payen, 1998 ¹⁹	247	Different doses of IFN	SVR	Pretreatment Knodell index	mean 0.76	.015
Zeuzem, 2000 ²⁰	120	IFN/AMA vs. IFN	SVR	Fibrosis	NR	NS
Angelico, 2000 ²¹	65	IFN/Col vs. IFN	Biochemical response‡	Low stage	NR	.036
				Low grade	NR	.49

Abbreviations: AMA, amantadine; Col, colchicine; IFN, standard interferon; PEG, peginterferon; RBV, ribavirin; SBR, sustained biochemical response; NR, not reported, NS, not significant.

*Text reported statistic was significant, but did not report P value.

†Estimate of Cox Proportional Hazard.

‡Similar results found for SVR, but data not presented.

nificant predictor of treatment response.¹⁹ In another study, the HAI was not a predictor of response.¹⁸

In the study evaluating standard interferon and amantadine, pretreatment histological findings were not associated with virological response to therapy.²⁰ In the study of standard interferon and colchicine, however, lower stage on pretreatment biopsy did predict a biochemical response to treatment in multivariate analysis. In this study, lower grade did not predict biochemical response to treatment.²¹

Results of Other Univariate Analyses. Seven other studies performed univariate analyses to assess the association between initial liver biopsy results and virological or histological outcomes, including 4 studies of standard interferon alone,²²⁻²⁵ 2 studies of standard interferon with ribavirin,^{26,27} and 1 study of standard interferon with amantadine versus standard interferon alone.²⁸

The results of the studies with standard interferon alone were mixed, with 1 study demonstrating a significant association between baseline histology and response to treatment,²³ 2 studies demonstrating no association between pretreatment biopsy findings and treatment response,^{22,25} and 1 study demonstrating a significant association of pretreatment biopsy findings with biochemical response, but not with virological or histological outcomes.²⁴ In the study with standard interferon and aman-

tidine²⁸ and the studies of interferon and ribavirin,^{26,27} pretreatment biopsy findings did not predict virological response to treatment.

Results of Analyses Stratified by Outcome. When the analysis of the relation between biopsy results and outcome was stratified by outcome, results were mixed. One study that stratified by outcome evaluated 3 different types of interferon (recombinant, leukocyte, and fibroblast).²⁹ In this study, sustained responders had lower baseline HAI scores than did nonresponders, both within each treatment group and compared with other groups, but the actual HAI scores were presented only as graphic data.²⁹

Results of Analyses Stratified by Treatment. Two studies stratified results by treatment group. One study examined standard interferon with and without ribavirin,¹¹ and the other compared standard interferon with peginterferon.³⁰ In the interferon and ribavirin study, pretreatment histological results did not predict response in the group treated with standard interferon and ribavirin, but fibrosis stage did predict response in the interferon-alone group.¹¹ In the study comparing standard interferon with peginterferon, the virological response was similar in those patients with bridging fibrosis and those with cirrhosis. In addition, baseline HAI scores were not predictive of virological response.³⁰

Other Data on Relation of Biopsy Results to Outcomes of Treatment. Six studies reported enough data to permit a multivariate logistic regression analysis of the relation of pretreatment liver histology to the effect of the treatment regimens on the SVR rate.^{11,12,20,28,30} The resulting analyses indicated that pretreatment histology was not consistently associated with a significant independent effect on SVR rate, although there was a trend in that direction. The studies were relatively consistent in finding no interaction between pretreatment fibrosis stage and the virological efficacies of different treatment regimens. Details of these analyses are included in our comprehensive evidence report.⁷

Summary. Taken together the evidence from these studies was relatively, but not entirely, consistent in finding that the presence of advanced fibrosis or cirrhosis may predict a modest decrease in the likelihood of having an SVR (Evidence Grade B).

Tests for Predicting Biopsy Findings

Characteristics of Studies. Sixty-six studies met our eligibility criteria for question 2 (although only 40 of these studies had enough data to be included in Table 2).³¹ Overall,^{24,32-69} the percentage of patients with genotype 1b ranged from 26% to 92%. The most common exclusion criteria in these studies were evidence of hepatitis B infection, heavy alcohol use, presence of other liver diseases, previous antiviral treatment, immune system disorders, and HIV infection.

Most of the studies used a cross-sectional or diagnostic test design, but a few studies used a prospective cohort design. In a few studies, a first set of patients was used to develop a statistical model predicting fibrosis, and the results were validated in an independent second set of patients.^{61,70,71} The mean age of the study populations ranged from 31 to 65 years. The percentage of subjects that were male ranged from 30% to 58%. The mean fibrosis score by the modified histological activity system ranged from 34% to 94%. Histological evidence of liver fibrosis was evaluated with several different staging systems.⁴

Quality of Studies. The median overall quality score for the studies on question 2 was 62% with a range from 11% to 88%. Most studies had scores \geq 75% for the study quality categories of representativeness, bias and confounding, and statistical analysis. The scores for description of the liver biopsy methods were low, because very few studies reported details on the type of needle biopsy and size of the liver core. Few studies had scores \geq 75% for the category of outcome assessment, and none of the studies reported on adverse effects of liver biopsy.

Results of Studies on Serum Aminotransferases. Serum ALT was the most commonly investigated marker.^{46,52,54,59-61,63,64,67,72-77} It was associated with fibrosis stage in 11 of 15 studies,^{46,52,54,59-61,63,74-77} with sensitivity ranging from 61% to 71%,^{46,52} and specificity ranging from 66% to 94%.^{46,52} Serum ALT as a single marker of fibrosis showed areas under the curve of 0.75 or less by receiver operating characteristic (ROC) analysis.^{52,54,61} Multivariate models of predictors of fibrosis incorporated serum ALT in 2 studies.^{59,61} In contrast, the ratio of aspartate aminotransferase (AST) to ALT had a sensitivity ranging from 31% to 56% and specificity of 90% to 100%.^{58,62,65,66} Little information was reported on the role of the AST/ALT ratio in predicting non-cirrhotic stages of fibrosis.

We concluded that the studies were relatively consistent in showing that serum aminotransferases have only modest value in predicting fibrosis on liver biopsy (Evidence Grade B).

Results of Studies on Extracellular Matrix Tests. Twenty-six studies investigated components of the extracellular matrix and/or markers of extracellular matrix degradation (see Table 2). Although these markers showed broad overlap for any given fibrosis stage, they were associated with fibrosis in every study examined, except for one study in which P-III-P was not associated with fibrosis.³⁴ Hyaluronic acid correlated best with fibrosis stage overall, with correlation coefficients ranging from 0.27 to 0.79, sensitivities ranging from 10% to 88% and specificities ranging from 59% to 100%. Laminin had sensitivities of 57% to 80% with specificities of 78% to 85%. Correlation coefficients ranged from 0.03 to 0.53 for type III collagen peptides and from 0.24 to 0.48 for type IV collagen peptides. Sensitivities of type III collagen peptides ranged from 24% to 89% and specificities from 38% to 88%. Markers of extracellular matrix degradation, such as tissue inhibitor of metalloproteinase-1-4, were also associated with fibrosis as single markers, but generally were less predictive than hyaluronic acid.

We concluded that these studies were relatively consistent in showing that hyaluronic acid and laminin may have value in predicting fibrosis on liver biopsy (Evidence Grade B).

Results of Studies on Other Tests. A number of cytokines and cytokine receptors were also investigated, including tumor necrosis factors (TNF), TNF-R55, TNF-R75, and TNF- α ,⁷⁸ as well as serum interleukin (IL) 2 receptors.⁷⁹ Except for TNF- α , the cytokine and cytokine receptors were associated with fibrosis, but were less predictive than markers of extracellular matrix. In contrast, TNF- α was associated with hepatic inflammation, but not with fibrosis.

Table 2. Relation of Biochemical and Serological Tests to Fibrosis on Liver Biopsy

Author, Year	N	Study Quality Score	Serologic Measure	Threshold Value*	Statistical Tests of Relation to Fibrosis on Biopsy				
					Correlation Coefficient		ROC Curve Area	Sensitivity	Specificity
					Statistic†	Result			
Casari, 2000	183	44	Laminin		Sp	0.44‡			
			NP-III-P		Sp	0.30‡			
Fukuda, 1998	36	45	HA		Pr	0.78‡			
			Type IV collagen		Pr	0.38‡			
Gabrielli, 1997	139	82	Laminin (P1)	1.8	Sp	0.40‡		57	78
			NP-III-P	1.0	Sp	0.34‡		24	88
Giannini, 2001	109	84	P-III-P		Sp	0.03			
Guechot, 1994	176	45	HA		Sp	0.47		55	92
			P-III-NP		Sp	0.18		40	66
Guechot, 1996	326	55	HA§	85	Unk	0.58	0.86	65	91
			P-III-P§	0.8	Unk	0.34		70	63
Ikeda, 2000	205	58	IgG		M	0.57			
			Platelets		M	-0.43		81	90
			HA		M	0.42			
			Gender		M	-0.21			
Ishibashi, 1996	121	50	HA		Sp	0.51‡			
			IV-7S		Sp	0.42‡			
			P-III-NP		Sp	0.33‡			
Jeffers, 1995	86	69	P-III-P		Sp	NS		58	82
			ALT		Sp	NS			
			HCV-RNA		Sp	NS			
Kasahara, 1997	98	62	MMP-1		Sp	NS			
			MMP-2		Sp	0.26‡			
			TIMP-1		Sp	0.30‡			
			TIMP-2		Sp	NS			
Lichtinghagen, 2000	80	53	MMP-2		Sp	NS			
			MMP-9		Sp	NS			
			Ratio of MMP-2:TIMP-1		Sp	-0.38			
			Ratio of MMP-9:TIMP-2		Sp	NS			
			TIMP-1		Sp	NS			
			TIMP-2		Sp	NS			
Lichtinghagen, 2001	46	56	MMP-2		Sp	0.52‡	0.77		
			MMP-7		Sp	0.53‡	0.75		
			MMP-9		Sp	0.39‡	0.68		
			TIMP-1		Sp	0.46‡	0.76		
			TIMP-2		Sp	0.34‡	0.66		
			TIMP-3		Sp	NS	0.55		
Lo Iacono, 1998	52	71	P-III-P	10.6	Pr		0.73	89	52
			sICAM-1	520	Pr		0.75	64	56
			sVCAM-1	1,280	Pr		0.96	100	85
McHutchison, 2000	486	70	HA	60				88	59
			HA	80				83	72
			HA	100				76	82
			HA	110				73	83
Murawaki, 1999	176	50	IV-C7S	8.5				82	85
			Hyaluronate	100				91	93
			Type IV collagen	150				85	81
			MMP-2	700				91	89
Murawaki, 2001	165	70	Platelets	14×10^4				68	74
			Platelets	16×10^4				68	71
			Type IV collagen	110				77	73
			Type IV collagen	130				66	75
Murawaki, 2001	169	60	ALT	80				61	66
			HA	50				75	80
			HA	70				50	79
			P-IV-NP	6				70	73
			P-IV-NP	6.5				63	73
			MMP-2	550				75	70
			MMP-2	575				68	69

Table 2. Continued

Author, Year	N	Study Quality Score	Serologic Measure	Threshold Value*	Statistical Tests of Relation to Fibrosis on Biopsy				
					Correlation Coefficient		ROC Curve Area	Sensitivity	Specificity
					Statistic†	Result			
Ninomiya, 1998	49	40	P-III-NP	0.8				74	52
			P-III-NP	0.9			64	59	
			TIMP-1	160			79	56	
			TIMP-1	170			82	54	
			HA¶		Sp	0.61‡			
			HA#		Sp	0.56‡			
			P-III-P¶		Sp	0.53‡			
			P-III-P#		Sp	0.51‡			
Ohashi, 1998	62	56	Type IV collagen¶		Sp	0.24			
			Type IV collagen#		Sp	0.32‡			
			Type IV collagen		Unk	0.48‡			
			HA		Unk	0.24			
Plevris, 2000	221	76	P-III-P		Unk	0.53‡			
			HA	50			83	60	
			HA	100			72	98	
			HA	200			67	99	
			HA	300			47	100	
Ueno, 2001	52	74	HA	400			10	100	
			HA**		Sp	0.29‡			
			HA††		Sp	0.46‡			
			P-III-P**		Sp	0.33‡			
			P-III-P††		Sp	0.39‡			
			Type IV collagen**		Sp	0.35‡			
			Type IV collagen††		Sp	0.26			
Verbaan, 1997	109	88	Ig G		Sp	0.43‡			
			P-III-P	1.1	Sp	0.32‡	78	56	
			Type IV collagen	250	Sp	0.43‡	87	75	
Walsh, 1999	38	53	ALT	55	Unk	-0.19	0.51	71	44
			CIS P-III-P	0.8	Unk	0.53‡	0.76‡	50	88
			Orion P-III-P	4.2	Unk	0.33	0.67	85	38
Walsh, 1999	52	60	ALT	60	Unk		0.59	67	52
			MMP-2	860	Unk	NS	0.67	69	59
			TIMP-1	500	Unk	0.25	0.73‡	94	57
			TIMP2-2	102	Unk		0.73‡	85	47
Walsh, 2000	42	50	ALT		Unk	-0.04	0.54		
			Laminin	1.3	Unk	0.67‡	0.82‡	80	85
			Type IV collagen	148	Unk	0.45‡	0.83‡	80	80
Wong, 1998	130	66	ALT			NS		76	48
			GST			NS		48	39
			HA			NS		86	88
Yamada, 1996	35	62	HA		Sp	0.79‡			
			P-III-P		Sp	0.45‡			
			Type IV collagen		Sp	0.42‡			
Yamada, 1998	36	3662	HA		Sp	0.78‡			
			P-III-P			NS			
			Type IV collagen		Sp	0.38‡			
Anderson, 2000	133	34	AST/ALT ratio	1.0				31	99
Assy, 2000	79	64	ALT		M	0.51‡			
			AST		M	0.64‡			
Barbaro, 1996	156	77	CD4 plus T-cell count		Pr	0.02			
			H-GSH		Pr	0.76‡			
Imbert-Bismut, 2001	339	78	10 markers in logistic regression††				0.86		
			10 markers in logistic regression§§		0.89				
			6 markers in logistic regression††				0.84		
			6 markers in logistic regression§§				0.87		

Table 2. Continued

Author, Year	N	Study Quality Score	Serologic Measure	Threshold Value*	Statistical Tests of Relation to Fibrosis on Biopsy				
					Correlation Coefficient		ROC Curve Area	Sensitivity	Specificity
					Statistic†	Result			
Imperiale, 2000	177	55	AST/ALT ratio	1.0				56	90
McCormick, 1996	44	45	ALT		Sp	NS			
			HCV titer		Sp	0.35			
Michielsen, 1997	51	64	ALT		Sp	0.08			
			AST		Sp	0.29‡			
Park, 2000	153	50	AST/ALT	1.0				47	96
Sheth, 1998	139	56	AST/ALT	1.0				53	100
Stanley, 1996	100	78	ALT	Normal	Unk	NS			
Puoti, 1999	59	74	HCV RNA		Sp	0.43‡			
Bayati, 1998	200	48	AFP	17.8				35	99

Abbreviations: NP-III-P, amino terminal peptide of type III procollagen; HA, hyaluronic acid; Laminin (P1), pepsin resistant fragment of laminin; P-III-P, procollagen type III peptides; P-III-NP, N terminal peptides of type III procollagen; IgG, immunoglobulin; IV-7S, 7 S domain of type IV procollagen; ALT, alanine aminotransferase; HCV-RNA, hepatitis C virus ribonucleic acid; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of matrix metalloproteinase; sICAM-1, serum level of soluble intercellular adhesion molecule-1; sVCAM-1, serum of soluble vascular cell adhesion molecule-1; P-IV-NP, 7S fragment of type IV collagen; CIS P-III-P, manufactured by CIS, United Kingdom; Orion P-III-P, manufactured by Orion, Finland; GST, glutathione-S transferase; AST/ALT ratio; AST, aspartate aminotransferase; H-GSH, glutathione concentration in liver; HCV titer, hepatitis C virus titer; AFP, alpha fetoprotein.

*Units: U/mL: Laminin, P-III-P, NP-III-P, ALT. U/kg: type IV collagen. $\mu\text{g/L}$: HA. dL^{-1} : IgG. mm^{-3} : platelets. ng/mL : IV-7S, sICAM-1, sVCAM-1, MMP, type TIMP. $\mu\text{mol/g}$: H-GSH.

†Pr, Pearson's *r*; Sp, Spearman's; MV, multivariate; Unk, not specified; NS, no correlation coefficient given, but reported as nonsignificant ($P > .05$).

‡Correlation coefficient is statistically significant ($P < .05$).

§Extensive cirrhosis.

||For moderate to severe chronic active hepatitis or cirrhosis.

¶Before treatment.

#After treatment.

**Nonresponder.

††Complete responder.

‡‡1st year period.

§§2nd year period.

Other tests were investigated, including glutathione,⁶⁰ α fetoprotein,^{69,73,80} prothrombin time,^{70,71,76} pseudo-cholinesterase,⁷⁰ manganese superoxide dismutase,⁷⁰ β -N-galactosidase,⁷⁰ α -2-macroglobulin,⁷⁰ β -globulin,⁷⁰ albumin,^{70,76} γ glutamyl transpeptidase,^{70,71,76,81} bilirubin,^{61,71,76} lactate dehydrogenase,⁷⁶ AST,^{71,76} alkaline phosphatase,⁷⁶ white blood cell count,⁷⁶ creatinine,⁷¹ total bile acids,⁸¹ and immunoglobulin G.⁵¹ Similar to the cytokines, these tests frequently were associated with fibrosis. However, these markers were less useful as a group than the markers discussed above, and only limited data were available on these markers. The platelet count, an indicator of portal hypertension, was also a predictor of cirrhosis in 3 studies, both in isolation and in studies using panels of markers.

We concluded that cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy (Evidence Grade B).

Results of Studies on Test Panels. Five studies^{46,61,70,71,76} used large panels of markers and achieved the greatest predictive values, with sensitivities ranging

from 50% to 82% and specificities from 35% to 80%. Of these studies, a panel of matrix metalloprotein-2, 7S type IV collagen, and hyaluronic acid optimally predicted no fibrosis/minimal fibrosis, with a sensitivity of 68% and specificity of 73%. Up to 94% of cirrhotic patients could be correctly identified using multivariate models.⁷⁰ In another multivariate model using different markers, moderate to severe inflammation and/or bridging fibrosis or cirrhosis could be identified with a specificity of 95% and sensitivity of 52%.⁷¹

We concluded that panels of markers may have the greatest value in predicting the absence or no more than minimal fibrosis on biopsy and in predicting the presence of cirrhosis on biopsy (Evidence Grade B).

Other Results. Some studies reported the levels of their serologic marker by fibrosis stage. They uniformly reported broad overlap between each fibrosis stage, with a trend toward increased levels of the serologic marker with increasing levels of fibrosis. Because of the broad overlap for any given histological stage of fibrosis, the tests were best at predicting the absence of fibrosis (or minimal

fibrosis) or identifying those with advanced fibrosis or cirrhosis. Serologic tests were less effective in classifying intermediate stages of fibrosis.

Discussion

Our review demonstrated that evidence on the relation of pretreatment liver biopsy findings to treatment outcomes is heterogeneous and has important limitations. Specific limitations are lack of reporting of parameter estimates and confidence intervals from univariate and multivariate analysis, as well as limited evaluation of interaction effects between baseline histology and treatment. Another limitation was that some studies compared the presence and absence of cirrhosis, while others used different staging systems. Few studies discussed the complications of biopsy. Most studies presented results in terms of significance for a P value less than .05, but few presented adjusted parameter estimates and confidence intervals. While a P value of less than .05 indicates a greater chance of a significant relationship, a nonsignificant P value does not mean zero effect. In addition, none of the studies reported a multivariable analysis that examined the potential interaction between pretreatment histology and the effects of different treatment regimens. Finally, some investigators may have evaluated the relation of initial histology to virological outcomes, but they may not have reported data that did not show a significant relationship, thus biasing the literature towards positive results. Recognizing these limitations and using the studies with the strongest type of analysis for this key question (i.e., multivariate analysis), we found that these studies were relatively, but not entirely, consistent in suggesting that the presence of advanced fibrosis or cirrhosis may predict a modest decrease in the likelihood of having an SVR.

The existing evidence on the relation of pretreatment histology to outcomes of treatment for chronic hepatitis C has implications for the clinical decision about whether to obtain a liver biopsy before deciding on treatment. Clinicians may want to consider the lack of definitive evidence on the relation of pretreatment histology to outcomes of treatment when discussing the pros and cons of a liver biopsy with patients.

The evidence also was heterogeneous regarding the utility of biochemical and serologic tests in predicting fibrosis in liver biopsy specimens in chronic hepatitis C. The studies assessed numerous tests using a variety of methods for reporting results. Most of the studies had important limitations in 1 or more categories of study quality. Nonetheless, the studies were relatively consistent in showing that (1) serum aminotransferases have only modest value in predicting fibrosis on liver biopsy, (2) the

extracellular matrix tests, such as hyaluronic acid and laminin, may have value in predicting fibrosis on liver biopsy, (3) cytokines have less value than the extracellular matrix tests in predicting fibrosis on liver biopsy, and (4) panels of tests may have the greatest value in predicting the absence or no more than minimal fibrosis on liver biopsy and in predicting the presence of cirrhosis on biopsy. None of the tests consistently classify intermediate stages of fibrosis.

The evidence on the performance characteristics of biochemical and serologic blood tests to predict fibrosis also has implications for the clinical decision about whether to biopsy patients with hepatitis C. Clinicians may want to consider the varying sensitivities and specificities of tests that could be used to predict the presence of advanced fibrosis or cirrhosis (which seems to be associated with a modest decrease in response to treatment). Although available tests have important limitations, they could have a role in management of patients who are concerned about the risk or cost of a liver biopsy or in a clinical setting in which liver biopsy cannot be readily obtained.

Future Research Needs

Future treatment studies could strengthen the evidence on the role of liver biopsy by using liver biopsy findings in a comprehensive analysis of factors associated with a virological or histological response to therapy. These studies should use standard techniques for reporting the average size of biopsy samples and standardized histological reports of biopsy findings. The studies also should report the details of both univariate and multivariate analyses of the relation of initial biopsy findings to outcomes, including adjusted and unadjusted parameter estimates of the relation of each histological variable to the outcome variable, and whether the analysis considered potential interaction effects. Such studies would help to provide better estimates of the independent value of liver biopsy in predicting outcomes of treatment.

Future studies on alternatives to liver biopsy should give attention to the methodologic limitations we encountered in trying to extract meaningful information from published studies. In particular, the studies should provide enough details about the biopsy methods to convince readers of the adequacy of the reference standard. Future studies also should give more attention to the potential value of a panel of tests for predicting fibrosis on biopsy.

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