SUPPLEMENT ARTICLE

Role of Liver Biopsy in the Evaluation of Hepatitis C Virus Infection in HIV Coinfection

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Hepatitis C virus (HCV) coinfection is common in patients infected with human immunodeficiency virus (HIV), because the viruses share common routes of transmission. With the marked increase in life expectancy of HIV-infected patients associated with the use of highly active antiretroviral therapy, HCV infection has become a significant cause of morbidity and mortality in coinfected patients. As a result, there has been increasing attention to adequate assessment of HCV infection during the last several years. Unlike liver enzymes and HCV RNA levels, which can fluctuate widely and do not correlate with the severity of disease, liver biopsy has become the cornerstone in the evaluation of chronic HCV infection. However, there remain important questions and controversies related to adequately determining the histological severity of liver disease and the role of liver biopsy in HIV-HCV–coinfected patients.

Because of their common routes of transmission, coinfection with hepatitis C virus (HCV) and HIV is common [1–3]. With the marked increase in life expectancy of HIV-infected patients associated with the use of highly active antiretroviral therapy (HAART) [4], HCV has become a significant cause of morbidity and mortality in coinfected patients [5–9]. In addition, HCV is associated with increased incidence of hepatotoxicity due to HAART [10, 11]. As a result, there has been increasing attention to adequate assessment of HCV infection during the last several years. Unlike liver enzymes and HCV RNA levels, which can fluctuate widely and do not correlate with the severity of disease, liver biopsy has become the cornerstone in the evaluation of chronic HCV infection. However, there remain important questions and controversies related to adequately determining the histological severity of liver disease in HIV-HCV–coinfected patients. This review highlights several of these issues, including the role of liver biopsy and the use of noninvasive tests to predict hepatic fibrosis, as well as the spectrum of liver disease and the effect of HAART on the natural history of HCV in coinfection with HIV.

LIVER BIOPSY

Liver biopsy is currently the reference standard in the evaluation of histological severity of chronic liver disease [12, 13]. The usual purposes for biopsy include evaluation of unexplained elevations in liver enzyme levels, confirmation of the diagnosis of chronic liver disease or exclusion of allograft rejection in liver transplant recipients, assessment of liver inflammation and fibrosis, and collection of tissue for special studies (table 1). Relative contraindications for percutaneous liver biopsy are an uncooperative patient, impaired coagulation, thrombocytopenia, ascites, biliary obstruction, and vascular tumors.

As with any invasive procedure, the benefits gained from the information obtained from liver biopsy must outweigh the small but definite risks associate with the procedure (table 2). Liver biopsy remains the best way to adequately assess liver inflammation and liver fibrosis, as well as to exclude comorbid conditions such as hepatic steatosis [14]. Liver biopsy also provides baseline data that can be used to assess prognosis. In general, patients with mild inflammation and no fibrosis have an excellent prognosis, whereas those with significant

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Table 1. Usual indications for liver biopsy.

Indication
Investigate unexplained elevations in liver chemistry results
Confirm the diagnosis of chronic liver disease
Determine the grade and stage of disease
Determine the etiology of a liver mass
Assess allograft after liver transplantation
Obtain tissue for special studies (iron, copper, α_1-antitrypsin)

inflammation and bridging fibrosis are at a high risk of developing cirrhosis [15, 16]. As a result, accurate assessment of histology, both inflammation and fibrosis, is important not only for patients who might undergo therapy for HCV infection but also to serve as a baseline for comparison in patients who forego treatment.

Liver biopsy can be associated with anxiety (to both patient and physician) and postprocedure pain. However, pain is usually mild and easily controlled with analgesics. The major risks associated with liver biopsy include bleeding (∼1/500 cases), puncture of other organs (e.g., lung, colon, gallbladder, and kidney), and, rarely, death (0.03% of cases) [13, 17, 18]. To minimize these risks, ultrasound guidance is often used. For those with impaired coagulation and/or ascites, a transjugular approach can be used.

HISTOLOGICAL ANALYSIS OF LIVER TISSUE

Although the histologic findings are nonspecific, chronic HCV infection is characterized by hepatocellular injury and necrosis associated with portal inflammation by mononuclear cells, with eventual erosion beyond the limiting plate and spillover of inflammatory cells (predominantly lymphocytes) that involve the surrounding hepatocytes (called piecemeal necrosis or interface hepatitis), often with spotty lobular inflammation. Lymphoid follicles in the portal areas, fatty infiltration, and bile ductular changes can also be seen [19]. The development of fibrosis is variable and usually follows a progressive course, from portal, to bridging fibrosis, and, eventually, to cirrhosis. To help standardize assessment of histological severity, several semiquantitative scoring systems have been developed, such as the histological activity index (HAI) of Knodell et al. [20] and its modifications by Ishak et al. [21] and METAVIR [22]. Although there are subtle differences among these scoring systems, they all provide information to assess both inflammatory activity (or grade) and fibrosis (or stage) (table 3). The inflammation grade is determined by assessment of piecemeal necrosis, confluent necrosis, lobular inflammation, and portal inflammation, whereas fibrosis is graded from none to cirrhosis (table 3). One proposed limitation of the Knodell fibrosis score is its nonlinearity (0, 1, 3, and 4). To overcome this, both METAVIR [22] and Ishak et al. [21] include a linear fibrosis scale (METAVIR, 0–4; Ishak et al., 0–6). In general clinical terms, among all 3 scoring systems, advanced fibrosis includes both bridging fibrosis and cirrhosis. Because use of these scoring systems often varies among different pathology laboratories, it is often difficult, outside of clinical trials, to compare scores among patients from different centers.

SPECTRUM OF LIVER DISEASE IN HIV-HCV COINFECTION

Before the identification of HCV, early reports about liver histology in HIV-infected patients were limited to patients with either unexplained fever associated with hepatomegaly or abnormal levels of liver enzymes [23–28]. In the absence of hepatitis B virus, *Mycobacterium* species, or cytomegalovirus infections, the most common findings were nonspecific steatosis and granuloma [29], whereas typical features of chronic HCV infection were not present.

Several reports published both before [30–34] and after the institution of HAART [35–41] have described hepatic histological profiles in patients with HCV-HIV coinfection. Several reports included both biopsy and autopsy specimens, as well as specimens from HIV-negative, HCV-positive patients for comparison. Overall, most studies show that the histological severity appears worse in those with HIV-HCV coinfection, especially in those with low CD4 cell counts and history of alcohol abuse. However, a limitation of most of these trials was the inclusion only of patients with elevated liver enzymes or with obvious signs of liver disease. This is important, because almost 50% of patients with HIV-HCV coinfection can have normal alanine aminotransferase (ALT) levels at the time of biopsy [42, 43], compared with 20%–30% in HCV-monoinfected patients [44, 45]. In a recent study that included patients with and without abnormal ALT levels, the histological spectrum of liver disease was similar in coinfected patients and HCV-infected control subjects [42]. When coinfected patients were stratified by normal or abnormal ALT findings, no significant differences were seen in CD4 cell counts, HAI, or its inflammation or fibrosis components. In particular, the prev-

Table 2. Risks and benefits of liver biopsy.

Risks	Benefits
Bleeding	Assess inflammation (grade)
Pain	Assess fibrosis (stage)
Puncture of organs	Rule out comorbid conditions
Sample error	
Financial cost	
Anxiety	
Death	

Table 3. Comparison of 3 histological scoring systems.

Grade or stage, parameter	Knodell et al. [20]	Ishak et al. [22]	METAVIR [22]
Inflammation			
Periportal necrosis[a]			
None	0	0	0
Mild	1	1	1
Mild/moderate		2	
Moderate (<50%)	3	3	2
Severe (>50%)	4	4	3
Confluent necrosis[a]			
None		0	0
Focal		1	
Zone 3 (some)	2		
Zone 3 (most)		3	
Portal-central bridging (some)	5	4	1
Portal-central bridging (marked)	6	5	
Panacinar	10	6	
Lobular necrosis			
None	0	0	0
Mild	1	1	0
Mild/moderate		2	1
Moderate	3	3	1
Severe	4	4	2
Portal inflammation			
None	0	0	0
Mild	1	1	1
Mild/moderate		2	1
Moderate	3	3	2
Severe (lymphoid aggregate)	4	4	3
Fibrosis			
None	0	0	0
Portal (some)	1	1	1
Portal (most)	1	2	1
Bridging (some)	3	3	2
Bridging (most)	3	4	3
Cirrhosis (incomplete)	4	5	4
Cirrhosis (complete)	4	6	4

[a] Knodell et al. combine periportal inflammation and bridging necrosis (score 0–10), whereas Ishak et al. assess them separately (0–4 and 0–6, respectively), and METAVIR primarily looks at periportal necrosis (0–3) with either the absence (0) or presence (1) of confluent necrosis.

alence of advanced fibrosis (i.e., bridging fibrosis or cirrhosis) in patients with normal ALT levels was 26% and highlights the importance of liver biopsy in this subset of coinfected patients.

EFFECT OF ANTIRETROVIRAL THERAPY ON THE NATURAL HISTORY AND HISTOLOGICAL SPECTRUM OF HCV INFECTION

There are limited data on the effect of specific antiretroviral agents on HCV in coinfected patients. In a retrospective analysis, Benhamou et al. [36] observed that, along with young age at infection, heavy alcohol consumption and a high CD4 cell count in patients whose HAART regimen did not contain a protease inhibitor (PI) had higher inflammation and fibrosis scores than did patients who took a PI as part of their HAART regimen. In contrast, a recent study was unable to detect any significant differences in the spectrum of liver disease in patients whose HAART regimen contained a PI and those whose regimen did not [43]. These discordant results may have been due to differences in the populations studied, patient demographics, alcohol use, and the dynamic changes that have occurred in anti-HIV therapy. In the study of Benhamou et al. [36], information about use of nonnucleoside reverse-transcriptase inhibitors (NNRTIs) in the PI treatment group was not given. Among 119 patients not taking a PI, 76 (66%) were taking nucleoside reverse-transcriptase inhibitors (NRTIs) alone, 40 (33%) were taking no antiretroviral medications, and only 3 patients were taking both NRTIs and NNRTIs. Furthermore, patients taking a PI had lower CD4 cell counts than did patients not taking a PI (mean, 286 vs. 399 cells/mm^3; $P = .001$). Therefore, it is unclear whether use of PIs themselves or the lower CD4 cell count accounted for less histological damage observed, because no patients with cirrhosis had <200 CD4 cells/mm^3 [43]. In both studies, the retrospective designs did not allow for the control of antiretroviral medications and the use of PIs to manage the HIV infection. However, given the rapid evolution of anti-HIV treatment, it is not possible to compare results of the 2 studies. In addition, both studies used a single-time biopsy, which limits the assessment of the true long-term impact of specific classes of antiretroviral medications on the natural history of HCV. Therefore, if these factors are taken into account, the results are less discordant, and perhaps effective HAART itself and not the use of PIs results in a spectrum of liver disease similar to that in an HIV-uninfected HCV-infected population.

There are few, if any, data about the effect of other specific classes of antiretroviral agents on the spectrum of liver disease in coinfected patients. When the effect of NNRTIs was examined, those patients whose HAART regimen included an NNRTI had lower HIV RNA levels and CD4 cell counts, and a higher proportion had undetectable HIV RNA than did those who did not take an NNRTI; no differences in liver histology between groups were seen [43]. However, because of provider bias in selection of HAART regimens, the clinical significance is unknown. Therefore, specific PI or NNRTI use may not be associated with obvious histological benefit nor obvious histological worsening of HCV disease. Finally, the use of higher doses of ritonavir in HIV therapy has been reported to be associated with increased hepatotoxicity in some [10] but not all [46, 47] studies.

NONINVASIVE MARKERS TO PREDICT LIVER HISTOLOGICAL PROFILE

Because of concerns over the small but known risks and inconveniences associated with liver biopsy, several investigators have explored the use of noninvasive markers to predict liver histology (reviewed by Fontana and Lok [48] and Gebo et al. [12]). Ideally, these tests should be simple, readily available, inexpensive, reproducible, sensitive to the effects of treatment, accurate in predicting the full spectrum of liver disease, and useful in tracking disease progression [48]. Most studies have looked for "surrogate" markers to primarily predict hepatic fibrosis and have largely ignored necroinflammation, which has been associated with progression of fibrosis [15, 16]. The most commonly investigated markers are serum aminotransferases (aspartate aminotransferase and ALT), which show only moderate ability to predict fibrosis (sensitivity, 30%–60%; specificity, 60%–100%). Other routine tests, such as prothrombin time and measurements of albumin and bilirubin, which reflect hepatic function, are insensitive, because results of these remain normal in patients until decompensation of liver disease develops. Other markers, such as extracellular matrix proteins (e.g., laminin, procollagen peptide III, hyaluronic acid, and YKL-40), give somewhat similar but varying results.

Because no single test will accurately be able to predict histology, several investigators have examined panels of tests. A panel based on patients' age and sex, combined with 5 biochemical markers (i.e., bilirubin, haptoglobin, γ-glutamyl transpeptidase, α_2-macroglobulin, and apolipoprotein A–I), has been developed. An index of 0–0.10 had high negative predictive value (100%), whereas an index of 0.60–1.00 had >90% positive predictive value to identify fibrosis graded as F2–F4 by use of the METAVIR scale [49]. This index has several limitations, because 50% of patients fell into an intermediate zone (index, 0.20–0.50), the index was not able to differentiate F2 from F3 and F4 fibrosis, and it used biochemical tests that are not readily available [48]. More recently, Wai et al. [50] developed a simple noninvasive index that used readily available routine tests; this index had high accuracy in predicting significant fibrosis in patients with chronic HCV infection. This aspartate aminotransferase-to-platelet ratio index (APRI) was able to accurately predict significant fibrosis in 51% and cirrhosis in 81% of patients.

The applicability of these models to coinfected patients is limited. Myers et al. [51] recently reported the utility of the 5-marker index described above in differentiating F0–F1 from F2–F4 fibrosis in a cohort of 130 coinfected patients and found a positive predictive value of 86% for an index of 0.60–1.00 and a negative predictive value of 93% for an index of 0.0–0.20. We have recently applied the APRI to a cohort of 119 coinfected patients with similar results [52].

CONCLUSIONS

There remain several unanswered questions with regard to the role played by liver biopsy in assessing histological severity of HCV infection in the setting of HIV coinfection. First and foremost, is liver biopsy needed for all coinfected patients? Existing data suggest that noninvasive tests to differentiate patients with little or no fibrosis from patients with advanced fibrosis may be applicable to just over half of coinfected patients. Furthermore, noninvasive tests do not accurately assess necroinflammation, which provides important prognostic information on the progression of fibrosis. Perhaps these noninvasive tests can be used to follow patients once a baseline histological profile is adequately determined, thus avoiding a second biopsy. The second question relates to timing of biopsy: Is it necessary before treatment or just for patients who do not respond to treatment? Given the increased responsiveness to treatment of HCV genotype 2/3, some researchers have advocated a "treat without biopsy" strategy in this small subset of coinfected patients [53]. Finally, many coinfected patients have significant psychiatric comorbidity and/or ongoing substance abuse. The decision to treat these "high-risk" patients is beyond the scope of the present article. However, controversies remain whether these patients should undergo liver biopsy if treatment is not anticipated. Although not perfect, noninvasive tests may also play a role for these patients. The management of HIV-HCV coinfection requires a concerted effort between infectious diseases specialists and hepatologists, often in collaboration with experts in mental health and addiction medicine. Given the effect of HCV on morbidity and mortality, the complexities of therapy for both HIV and HCV infection, and the current limitations of noninvasive markers, liver biopsy continues to play an important role in the evaluation of HCV infection in the setting of HIV coinfection.

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