ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

Complication Rate of Percutaneous Liver Biopsies Among Persons With Advanced Chronic Liver Disease in the HALT-C Trial

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Podcast interview: www.gastro.org/cghpodcast; see related article, West J and Card TR, on page 1230 in *Gastroenterology*; see Editorial on page 826.

BACKGROUND & AIMS: Although percutaneous liver biopsy is a standard diagnostic procedure, it has drawbacks, including risk of serious complications. It is not known whether persons with advanced chronic liver disease have a greater risk of complications from liver biopsy than patients with more mild, chronic liver disease. The safety and complications of liver biopsy were examined in patients with hepatitis C–related bridging fibrosis or cirrhosis who were enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis trial. **METHODS:** Standard case report forms from 2740 liver biopsies performed at 10 study sites between 2000 and 2006 were reviewed for serious adverse events, together with information from questionnaires completed by investigators about details of biopsy techniques used at each hospital. **RESULTS:** There were 29 serious adverse events (1.1%); the most common was bleeding (16 cases; 0.6%). There were no biopsy-related deaths. The bleeding rate was higher among patients with platelet counts of 60,000/mm^3 or less and among those with an international normalized ratio of 1.3 or greater, although none of the patients with an international normalized ratio greater than 1.5 bled. Excluding subjects with a platelet count of 60,000/mm^3 or less would have reduced the bleeding rate by 25% (4 of 16), eliminating only 2.8% (77 of 2740) of biopsies. Operator experience, the type of needle used, or the performance of the biopsy under ultrasound guidance did not influence the frequencies of adverse events. **CONCLUSIONS: Approximately 0.5% of persons with hepatitis C and advanced fibrosis experienced potentially serious bleeding after liver biopsy; risk increased significantly in patients with platelet counts of 60,000/mm^3 or less.**

Keywords: Liver Biopsy; Complications; Adverse Event; Serious Adverse Events; Bleeding; Platelet Count; INR.

A liver biopsy provides important diagnostic and management information in unexplained acute and chronic liver diseases.[1] It is necessary for grading and staging disease and for assessing treatment response in persons with chronic hepatitis C virus infection,[1] and is helpful in identifying other conditions that may affect chronic hepatitis C outcome, such as hepatic steatosis[2] and iron content.[3] However, support for a liver biopsy in chronic hepatitis C has declined recently as therapy has improved and noninvasive tests for fibrosis have been developed.[4] Other reasons for its falling status include the risk of complications,[1,5,6] sampling variability,[7] procedural anxiety and discomfort, and its added cost. Nevertheless, the Food and Drug Administration requires liver histology as a primary therapeutic end point in clinical trials of new therapies for chronic liver disease, and it will likely be an end point for future therapeutic trials of antifibrotic agents.

Numerous reports detail the safety and complication rate of liver biopsy performed with or without ultrasound guidance. Minor complications include pain at the biopsy site or vasovagal episodes [6,8–14] The most commonly reported and concerning major complication is bleeding, occurring in 0.8% to 1.7% of liver biopsies.[6,8–14,15,16] Although death is rare, ranging from 0% to 0.14%,[6,8–11,13,14] a higher rate (0.33%) was reported in one study.[12] The complication risk is presumed to be higher in patients with advanced liver disease, but detailed analysis of biopsy complications in such patients is lacking.

The Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial, designed to evaluate the safety and efficacy of long-term, low-dose maintenance therapy with peginterferon alfa-2a in patients with advanced chronic hepatitis C, provided a unique opportunity to assess the risk of liver biopsy

Abbreviations used in this paper: AE, adverse event; HALT-C, Hepatitis C Antiviral Long-Term Treatment against Cirrhosis; INR, international normalized ratio; PT, prothrombin time; SAE, serious adverse event.

1542-3565/$36.00
doi:10.1016/j.cgh.2010.03.025

in these patients.[17] Enrollment requirements included liver biopsies at baseline, at 1.5 years, and at 3.5 years, provided no clinical outcome had occurred and no contraindications to biopsy had developed.

The primary aim of this analysis was to assess the number and types of liver biopsy complications among the HALT-C patients with advanced liver disease. The prestudy hypothesis was that the complication rate would be higher in persons with histologically defined cirrhosis than with bridging fibrosis alone, and that the rate would be higher than in previously reported studies involving patients with a milder degree of disease severity.

Methods

The HALT-C trial was conducted at 10 clinical sites between August 2000 and July 2006.[17] Inclusion criteria were age older than 18 years, compensated chronic hepatitis C, and nonresponse to prior treatment with interferon with or without ribavirin. Exclusion criteria were a Child–Turcotte–Pugh score of 7 or greater, platelet count less than 50,000/mm^3, hemoglobin level less than 11 g/dL, serum creatinine level greater than 1.5 mg/dL, α-fetoprotein level greater than 200 ng/mL, a mass on imaging suggesting hepatocellular carcinoma, or any serious medical condition that might compromise participation for up to 4 years. Patients must have had a liver biopsy within 12 months of enrollment, which was graded for inflammation using the modified histology activity index score and for fibrosis using the Ishak et al[18] scoring system by consensus face-to-face vote of the 10 clinical site hepatopathologists and a coordinating pathologist from the Armed Forces Institute of Pathology. The baseline biopsy was required to have an Ishak fibrosis score of 3 or greater (bridging fibrosis or cirrhosis) or a score of 2 at baseline provided a prior liver biopsy had an Ishak fibrosis score of 3 or greater.

If serum hepatitis C virus RNA persisted 20 weeks after treatment with 180 μg weekly peginterferon alfa-2a (Pegasys; Roche Pharmaceuticals, Nutley, NS), and 1000/1200 mg/d ribavirin (Copegus; Roche Pharmaceuticals), patients were randomized at week 24 to no treatment (control group) or to continue treatment as lead-in patients with peginterferon alfa-2a alone (90 μg/wk subcutaneously). The protocol later was modified, permitting randomization of nonresponder patients to at least 24 weeks of peginterferon and ribavirin treatment outside of the HALT-C trial, provided they met the inclusion and exclusion criteria (express patients), as well as responders to lead-in therapy who broke through during the remaining 48-week course of combination therapy or who relapsed after completing the 48 weeks of combination therapy (breakthrough/relapse patients).[17]

Patients were seen every 3 months for history taking, physical examination, and laboratory testing to monitor the peginterferon therapy and assess for clinical end points and adverse events. A repeat liver biopsy was required 18 months after randomization (24 months after enrollment for lead-in patients) and again 42 months after randomization (48 months after enrollment for lead-in patients).

Although almost all baseline biopsies were performed at HALT-C study sites, all biopsies at 1.5 and 3.5 years after randomization were performed at HALT-C sites. Data analysis was confined to percutaneously performed biopsies at HALT-C sites, excluding 11 biopsies obtained via the transjugular route.

Preparations for and methods used to perform liver biopsies were not recorded at the actual time of the procedure. Subsequently, principal investigators at each participating center completed a questionnaire regarding these requirements. Information collected included the identity of the person who performed the biopsy (principal investigator, gastroenterology/hepatology fellow, or radiologist), whether it was an inpatient or outpatient procedure, whether ultrasonography was used, whether the liver surface routinely was anesthetized, what type and diameter of biopsy needle was used, the number of passes usually performed, whether conscious sedation was used, when aspirin and/or nonsteroidal anti-inflammatory drugs were discontinued before biopsy, what blood tests and coagulation parameters were required in preparation for the biopsy, whether a routine complete blood count was performed postliver biopsy, and the postbiopsy observation period required before discharging the patient.

Complications of the procedure were collected prospectively by study coordinators and submitted to the Data Coordinating Center. Nonserious adverse events (AEs) were defined as symptoms believed to be related to the biopsy not requiring hospitalization. Serious adverse events (SAE) were defined as complications requiring hospitalization, additional costly investigations (ultrasound, computed tomography, endoscopic retrograde cholangiopancreatography), a blood transfusion, or complications that led to perforation of an organ, surgery, or death. All AEs and SAEs occurring within 30 days after the liver biopsy were reviewed to determine their relationship to the biopsy.

Statistical Methods

Data were analyzed with SAS software (Statistical Analysis Software, version 9.1; SAS Institute, Cary, NC). Chi-square and *t* tests were used to calculate the significance of differences in variables between No Complications and All SAE groups, and No Complication and Bleeding Complication groups.

Results

Preparations for and Techniques of the Liver Biopsies

Questionnaire responses indicated that biopsies were performed predominantly by participating HALT-C investigators, all experienced hepatologists, but an estimated 20% were performed by supervised gastroenterology/hepatology fellows, and, occasionally, by interventional radiologists. Approximately 90% were outpatient procedures. Most (80%) used bedside ultrasound guidance, and all included anesthetizing the subcutaneous tissue and liver capsule. In 60%, conscious sedation with short-acting benzodiazepines was used. Forty percent of biopsies were performed with an aspiration needle and 60% were performed with a cutting needle, mostly with 16-gauge needles. A single pass was performed in 40% of institutions, the remaining 60% using 2 passes routinely or commonly, attempting to obtain at least 1.5 cm of unfragmented liver tissue. All participants discontinued aspirin 7 to 14 days and nonsteroidal anti-inflammatory drugs 1 to 10 days before the biopsy. All centers required performance of a complete blood count, platelet count, and prothrombin time (PT) or international normalized ratio (INR). Forty percent required platelet counts of at least 70,000/mm^3 as a precondition for the biopsy, whereas the remaining 60% permitted biopsies with lower platelet counts,