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

Leonard B. Seeff, MD¹, Gregory T. Everson, MD², Timothy R. Morgan, MD³, Teresa M. Curto, MSW, MPH⁴, William M. Lee, MD⁵, Marc G. Ghany, MD⁶, Mitchell L. Shiffman, M.D.⁷, Robert J. Fontana, M.D.⁸, Adrian M. Di Bisceglie, M.D.⁹, Herbert L. Bonkovsky, M.D.¹⁰, and Jules L. Dienstag, M.D.¹¹ the HALT-C Trial Group

Leonard B. Seeff: seeffl@extra.niddk.nih.gov; Gregory T. Everson: greg.everson@ucdenver.edu; Timothy R. Morgan: timothy.morgan@va.gov; Teresa M. Curto: tcurto@neriscience.com; William M. Lee: William.Lee@UTSouthwestern.edu; Marc G. Ghany: MarcG@bdg10.niddk.nih.gov; Mitchell L. Shiffman: mlshiffman@gmail.com; Robert J. Fontana: rfontana@umich.edu; Adrian M. Di Bisceglie: dibiscam@slu.edu; Herbert L. Bonkovsky: Herbert.bonkovsky@carolinashealthcare.org; Jules L. Dienstag: jdienstag@partners.org

¹Division of Digestive Diseases and Nutrition, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

²Section of Hepatology, Division of Gastroenterology and Hepatology, University of Colorado Denver, School of Medicine, Aurora, CO

³Division of Gastroenterology, University of California - Irvine, Irvine, CA and Gastroenterology Service, VA Long Beach Healthcare System, Long Beach, CA

⁴New England Research Institutes, Watertown, MA

⁵Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX

⁶Liver Diseases Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, MD

⁷Liver Institute of Virginia, Bon Secours Health System, Newport News and Richmond, VA

⁸Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI

⁹Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St. Louis, MO

¹⁰Departments of Medicine and Molecular & Structural Biology and The Liver-Biliary-Pancreatic Center, University of Connecticut Health Center, Farmington, CT. (Dr. Bonkovsky's current address is Carolinas Medical Center, Charlotte, NC)

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Address correspondence to: Leonard B. Seeff, M.D., National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 31A Center Drive, Room 9A27, Bethesda MD 20892, Tel. No. 301-435-3338, Fax. No. 301-480-7926, seeffl@extra.niddk.nih.gov.

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¹¹Gastrointestinal Unit (Medical Services), Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston, MA

Abstract

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 that were enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial.

Methods—Standard case report forms from 2,740 liver biopsies performed at 10 study sites between 2000 and 2006 were reviewed for serious adverse events, along 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 $< 60,000/\text{mm}^3$ and among those with an international normalized ratio (INR) > 1.3 , although none of the patients with an INR > 1.5 bled. Excluding subjects with a platelet count $< 60,000/\text{mm}^3$ would have reduced the bleeding rate by 25% (4/16), eliminating only 2.8% (77/2740) 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 $< 60,000/\text{mm}^3$ (K2).

Keywords

liver biopsy; complications; adverse event; serious adverse events; bleeding; platelet count; INR

Introduction

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 (HCV) infection,¹ and is helpful in identifying other conditions that may affect chronic hepatitis C outcome, such as hepatic steatosis² and iron content.³ However, support for a liver biopsy in chronic hepatitis C has declined recently as therapy has improved and non-invasive 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 endpoint in clinical trials of new therapies for chronic liver disease, and it will likely be an endpoint 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 0.8-1.7% 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 in these patients.¹⁷ Enrollment requirements included liver biopsies at baseline, 1.5 and 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 pre-study 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 milder degree of disease severity.

Methods

The HALT-C Trial was conducted at 10 clinical sites between August 2000 and July 2006.²⁴ Inclusion criteria were age >18 years, compensated chronic hepatitis C, and nonresponse to prior treatment with interferon with or without ribavirin. Exclusion criteria were a Child-Turcotte-Pugh (CTP) score ≥ 7 , platelet count $<50,000/\text{mm}^3$, hemoglobin $<11\text{ g/dL}$, serum creatinine $>1.5\text{ mg/dL}$, AFP $>200\text{ ng/mL}$, a mass on imaging suggesting hepatocellular carcinoma (HCC) 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 (HAI) score and for fibrosis using the Ishak scoring system¹⁸ 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 ≥ 3 (bridging fibrosis or cirrhosis) or a score of 2 at baseline provided a prior liver biopsy had an Ishak fibrosis score of ≥ 3 .

If serum HCV RNA persisted 20 weeks after treatment with peginterferon alfa-2a (Pegasys, Roche Pharmaceuticals), 180 μg weekly and ribavirin (Copegus, Roche Pharmaceuticals), 1,000/1,200 mg/day, 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 subcutaneously every week). The protocol was later modified, permitting randomization of non-responder 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 three months for history taking, physical examination, and laboratory testing to monitor the peginterferon therapy and assess for clinical endpoints 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).

While 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 utilized; whether the liver surface was routinely anesthetized; what type and diameter of biopsy needle was used; the number of passes usually performed; whether conscious sedation was utilized; when aspirin and/or non-steroidal anti-inflammatory drugs (NSAIDs) 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 post-liver biopsy; and the post-biopsy observation period required before discharging the patient.

Complications of the procedure were collected prospectively by study coordinators and submitted to the Data Coordinating Center. Non-serious adverse events (AE) were defined as symptoms thought 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 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 (Statistical Analysis Software, version 9.1, SAS Institute, Cary, NC) software. Chi-squared 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 US guidance, and all included anesthetizing the subcutaneous tissue and liver capsule. In 60%, conscious sedation with short-acting benzodiazepines was utilized. Forty percent of biopsies were performed with an aspiration needle and 60% with a cutting needle, mostly with 16 gauge needles. A single pass was performed in 40% of institutions, the remaining 60% using two passes routinely or commonly, attempting to obtain at least 1.5 cm of unfragmented liver tissue. All participants discontinued aspirin seven to 14 days and NSAIDs one 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/mm³ as a precondition for the biopsy, while the remaining 60% permitted biopsies with lower platelet counts, in two-thirds of them as low as 50,000/mm³. Only 20% routinely checked the complete blood count post-procedure, and all but one institution allowed same-day discharge, generally within four to six hours.

Overall Complication Rate

The analysis comprised 2,740 percutaneous liver biopsies, 1187 at baseline, 852 at 1.5 years and 701 at 3.5 years after randomization (Table 1). Of the expected 1050 liver biopsies, 144 (14%) were not obtained at month 24 and 285 (27%) were not obtained at month 48. All three biopsies were accomplished in 523 (38%) patients, 309 (22%) had two biopsies, and 553 (40%) had only one biopsy performed. The one reason for missed biopsies (Table 2)

that might have modified the observed complication rate (see below) was withholding the procedure because of low platelet counts. In the 16 patients not biopsied at 1.5 years because of low platelet counts, the counts ranged from 30,000 to 73,000mm³ (8 with values of 50,000mm³), while in the 24 patients not biopsied at year 3.5 because of low platelet counts, the counts ranged from 26,000 to 69,000mm³ (10 with values 50,000mm³).

A liver biopsy complication was reported in 63 (2.3%) of the 2,740 biopsies performed (Table 1), 32 (2.7%) among the 1,187 baseline biopsies, 20 (2.3%) among the 852 performed at 1.5 years, and 11 (1.6%) among the 701 conducted at 3.5 years. Thirty-four (54%) of the 63 complications were classified as non-serious AEs, the remaining 29 biopsy complications categorized as SAEs. Most non-serious AEs (32/34; 94%) were transient pain at the biopsy site, while the remaining two were a localized hematoma at the biopsy site and inflammation at the IV cannula site. The development of an AE and an SAE was similar among patients who had received peginterferon within four weeks of the biopsy (AE, 10/550 [1.8%]; SAE, 5/545 [0.9%]) as among patients who had not received peginterferon within four weeks of the biopsy (AE, 53/2190 [1.9%]; SAE 24/2161 [1.1%]). Accordingly, data were combined for this analysis.

The overall frequency of SAEs was 1.1% (29/2,740) (Table 3) Bleeding accounted for 16 SAEs (55%), the remainder being severe pain in seven (24.1%) patients; a punctured gallbladder in two (6.9%); and in one patient (3.4%) each, marked hypotension, pneumothorax, syncope, and presumed dehydration (hypotension, without evidence of bleeding or a vasovagal reaction, responsive to fluids). The 16 bleeding episodes consisted of hemoperitoneum in eight, subcapsular hematoma in four, hemobilia in three and hemothorax in one. Four patients who bled required blood transfusions while eight were treated with embolization of the bleeding vessel and/or required surgery to evacuate the blood. One patient whose gallbladder was punctured underwent immediate laparoscopic cholecystectomy while the other had endoscopic bile duct stent placement. One patient had two SAEs, consisting first of severe pain after the baseline biopsy, and second of a subcapsular hematoma. No deaths occurred as a complication of liver biopsy.

The rates of SAEs were not significantly different across the centers (p=0.17) (Table 4).

Relationship of Selected Variables to the Occurrence of an SAE

Correlations of demographic, biochemical, and biopsy performance variables with the occurrence of all SAEs and of bleeding only are shown in Table 5. Significant associations with an SAE included a lower albumin level (median level for all SAE patients, 3.7 gm/L vs. non-SAE patients, 3.9 gm/L, $p < 0.02$), a platelet count of 60,000mm³, an INR 1.3, and the presence of any esophageal varices. The analysis correlating varices with SAEs was restricted to the second and third biopsies because upper endoscopies were performed an average of 41 weeks after the baseline biopsy, too late for a meaningful correlation. Approaching but not reaching significance was gender difference, biopsy by a fellow, and using more than one needle pass. No difference was detected in the SAE frequencies between biopsies with a cutting than an aspiration needle or between biopsies of patients with histologically-evident cirrhosis than bridging fibrosis.

The findings were almost identical for comparisons between the 2,677 biopsies with no complications and the 16 with SAEs confined to bleeding, with two exceptions (Table 5). In contrast to the analysis involving all SAEs, no correlation with *bleeding* SAEs was observed regarding the person who performed the biopsy or the number of passes made.

Because a low platelet count and an increased INR significantly affected the rate of bleeding (Tables 5), an effort was undertaken to identify cut-off values for these two indices that

correlated with bleeding (Tables 6 and 7). Bracketing by stepwise declining differences in platelet counts of 40,000 to 50,000/mm³, the bleeding frequency was found to range from 0.2% for platelet counts >150,000, to 0.7% for counts between 101,000 and 150,000, to 0.6% when the count was between 61,000 and 101,000, rising dramatically to 5.3% for platelet counts of 60,000/mm³ (Table 7). Similarly, the bleeding rate was 0.4% with an INR of 1.1, 1.1% with an INR of 1.2, increasing to 2.4% with an INR 1.3. No significant effect was noted in these comparisons for BMI, length of the biopsy specimen, fragmentation of the liver tissue, and presence or absence of splenomegaly.

Bleeding might conceivably have been the result of inadvertent needle puncture of vascular structures but no evidence for this was observed by expert pathologists who read the biopsies. If liver biopsies had been avoided when platelet counts were 60,000/mm³, bleeding as a complication would have been reduced by 25% (4/16), while eliminating only 2.8% (77/2740) of the biopsies.

Discussion

Deciding to perform a liver biopsy must take into account the value of information hoped to be gained relative to the risk of complications. Hepatic histology helps define liver disease etiology and severity and aids clinicians in management. Liver biopsy has accordingly been a cornerstone in evaluating persons with liver disease.¹ However, it is invasive, associated potentially with serious complications that rarely may be life-threatening.^{6,8-15}

In the HALT-C Trial,¹⁷ liver biopsies were performed largely by experienced hepatologists in outpatient facilities, mostly under ultrasonographic guidance, 60% of institutions administered conscious sedation and a cutting needle was slightly preferred. Patients were advised to discontinue aspirin one to two weeks and NSAIDs one to 10 days prior to the procedure. Pre-biopsy laboratory assessment included a complete blood count, activated partial thromboplastin time, and the prothrombin time or INR. Patients biopsied in outpatient facilities were discharged within 2 to 6 hours of the procedure. In one center, biopsies were performed as an inpatient procedure and the patient observed in the hospital overnight. Despite differences in procedures and clinical management, the SAE risk was not significantly different among the centers, although the bleeding frequency was higher in one than in the other nine centers.

Serious adverse events occurred in 1.1% of all liver biopsies undertaken. The risk of an SAE was similar for biopsies performed at baseline, at 1.5 and at 3.5 years after randomization. As expected,^{6,8-15} the most common SAE was bleeding (0.6%), accounting for 16 of the 29 SAEs. All but one bleeding episode came from the hepatic puncture site, causing a hemoperitoneum (0.3%), subcapsular hematoma (0.1%), or hemobilia (0.1%). Severe pain (0.3%) was the next most common complication requiring hospital admission for observation and pain management. Other SAEs were gallbladder puncture (0.07%) and pneumothorax (0.04%); no biopsy-related deaths occurred. The types and frequencies of SAEs in the HALT-C cohort were thus similar to those reported in other studies.

Baseline characteristics indicated that patients who experienced SAEs, particularly bleeding, had more advanced liver disease than those who did not have SAEs. Serum albumin concentrations and platelet counts were lower, INR was higher, and a greater proportion of these patients had endoscopically-proven varices. Interestingly, patients with histologically proven cirrhosis were no more likely than those with bridging fibrosis to develop an SAE, including bleeding.

Because bleeding was the most common SAE, a correlation was sought between results of the coagulation tests - platelet count and INR value - and bleeding. The bleeding risk was

0.4% for those with an INR of 1.1, 1.1% with an INR of 1.2, and 2.4% with an INR of 1.3. Of note is that none of the eight biopsied patients with INR values >1.5 experienced bleeding. This contrasts with results from a large retrospective survey of liver biopsy practices in the United Kingdom where the frequency of bleeding was 3.3% when the INR was between 1.3 and 1.5, but increased to 7.1% when the INR exceeded 1.5.¹⁴ These data notwithstanding, no recommendation can be made to use a prolonged prothrombin time (PT) or increased INR as markers of bleeding risk in persons with cirrhosis. As noted, several studies indicate that an abnormal PT in persons with cirrhosis is not a strong predictor of bleeding risk.¹⁹⁻²³ This observation is attributed to intricacies of the PT test which measures only pro-coagulant activity whereas persons with cirrhosis have a decrease in anti-coagulants as well as pro-coagulants.²⁴ Moreover, although INR calculation, designed to standardize the PT measurement,²⁵ is considered more robust than measuring the PT, there is strong evidence for variability in its measurement among different clinical laboratories [especially in patients with liver disease], thus limiting its value as a credible forecaster for biopsy-related bleeding.²⁶⁻²⁸

In contrast, a clear relationship was identified between the platelet count and the risk of bleeding. The risk was 0.2% when the platelet count exceeded 150,000/mm³, 0.6% to 0.7% for platelet counts between 150,000 and 61,000/mm³, increasing strikingly to 5.3% for platelet counts <60,000/mm³. Smaller studies involving persons with wider ranges of liver disease have reported similar low platelet count levels associated with an increased risk of bleeding,^{12,29} although there are studies that refute these observations.¹⁹ Nevertheless, we recommend caution when considering percutaneous liver biopsy in patients with a platelet count <60,000/mm³.

Regarding the liver biopsy technique, no procedural factor, including operator experience, the use of ultrasonographic guidance, the type of biopsy needle, or the number of passes made were definitively associated with an increased risk for an SAE. Others have also failed to detect the type of needle used as a risk factor,^{30,31} although the cutting needle appears to provide superior liver biopsy specimens.³¹ A trend was observed, however, toward a greater risk of a non-bleeding SAE if more than one pass was made or an inexperienced operator performed the procedure.

This study has several limitations. First, technical and procedural data were not recorded at the actual time of liver biopsy. Also, patients were not prospectively randomized for use of ultrasound, type of needle, and number of passes performed. Therefore, the lack of association with technical factors should be interpreted with caution. Second, because INR testing was not conducted in a central laboratory, the association between bleeding and increased INR values must also be viewed with caution, as noted above. Third, it is uncertain whether the results in this study involving individuals with advanced chronic hepatitis C can be applied to advanced chronic liver disease of other etiologies. Nevertheless, this study represents one of the largest series evaluating safety of liver biopsy in well-characterized patients with compensated chronic hepatitis C.

In summary, the performance and risks of liver biopsy have been carefully evaluated among patients in the HALT-C trial, a well defined cohort with advanced chronic hepatitis C. Despite their advanced chronic liver disease, liver biopsy in this group was safe and well tolerated with an overall SAE risk of 1.1% and no deaths. SAEs, particularly bleeding, were more frequent among patients with laboratory and endoscopic features of more advanced liver disease, although the presence of histologically-confirmed cirrhosis was not predictive. No liver biopsy technique or liver biopsy needle was more highly associated with the risk of bleeding or other serious adverse events. The analysis does suggest that percutaneous liver

biopsy in patients with a platelet count $60,000/\text{mm}^3$ carries an increased risk of bleeding and should be avoided.

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University of Massachusetts Medical Center, Worcester, MA: (Contract N01-DK-9-2326) Gyongyi Szabo, MD, Barbara F. Banner, MD, Maureen Cormier, RN, Donna Giansiracusa, RN

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University of Southern California, Los Angeles, CA: (Contract N01-DK-9-2325, Grant M01RR-00043) Karen L. Lindsay, MD, MMM, Jeffrey A. Kahn, MD, Sugantha Govindarajan, MD, Carol B. Jones, RN, Susan L. Milstein, RN

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Virginia Commonwealth University Health System, Richmond, VA: (Contract N01-DK-9-2322, Grant M01RR-00065) Richard K. Sterling, MD, MSc, Melissa J. Contos, MD, A. Scott Mills, MD, Charlotte Hofmann, RN, Paula Smith, RN

Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD: T. Jake Liang, MD, David Kleiner, MD, PhD, Yoon Park, RN, Elenita Rivera, RN, Vanessa Haynes-Williams, RN

National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition, Bethesda, MD: James E. Everhart, MD, Patricia R. Robuck, PhD, Jay H. Hoofnagle, MD, Elizabeth C. Wright, PhD

University of Washington, Seattle, WA: (Contract N01-DK-9-2318) Chihiro Morishima, MD, David R. Gretch, MD, PhD, Minjun Chung Apodaca, BS, ACP, Rohit Shankar, BC, ACP, Natalia Antonov, M. Ed.

New England Research Institutes, Watertown, MA: (Contract N01-DK-9-2328) Kristin K. Snow, MSc, ScD, Margaret C. Bell, MS, MPH

Armed Forces Institute of Pathology, Washington, DC: Zachary D. Goodman, MD, PhD, Fanny Monge, Michelle Parks

Data and Safety Monitoring Board Members: (Chair) Gary L. Davis, MD, Guadalupe Garcia-Tsao, MD, Michael Kutner, PhD, Stanley M. Lemon, MD, Robert P. Perrillo, MD

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Table 1

Liver Biopsy Complications

Timing of Biopsy	No. of Biopsies	Non-Serious Adverse Events		Serious Adverse Events	
		#	%	#	%
Screening	1187	21	1.8	11	0.9
Month 24	852	11	1.3	9	1.1
Month 48	701	2	0.3	9	1.3
Total	2740	34	1.2	29	1.1

Table 2
Numbers and Reasons for Missed Biopsies

	Month 24	Month 48
Number missed biopsies	144	285
Reasons missed (%)		
Outcome reached	27.8	43.2
Patient withdrew	31.9	28.4
Visits missed	11.8	7.4
Adverse event	9.0	5.3
Low platelets	11.1	8.4
Refused biopsy	8.3	7.4

Table 3
Description of Complications Recorded as a Serious Adverse Event Among 2740 Liver Biopsies Performed

Description	No. Serious Adverse Events	Percentages/Liver Biopsy	Percentages/Serious Adverse Event
Bleeding *	16	0.58%	55.2%
Severe pain	7	0.26%	24.1%
Punctured gall bladder	2	0.07%	6.9%
Marked hypotension	1	0.04%	3.4%
Pneumothorax	1	0.04%	3.4%
Syncope	1	0.04%	3.4%
Dehydration	1	0.04%	3.4%
Total	29	1.06%	100.0%

* Hemoperitoneum, 8 cases; subcapsular hematoma, 4 cases; hemobilia, 3 cases, hemothorax, 1 case

Table 4

Frequencies of Serious Adverse Events by Clinical Center

Clinical Center	No. Biopsies	Serious Adverse Event		Bleeding Complication	
		No.	%	No.	%
A	139	0	0	0	0
B	241	1	0.4	0	0
C	544	3	0.6	2	0.4
D	148	1	0.7	0	0
E	265	2	0.8	1	0.4
F	246	2	0.8	2	0.8
G	396	4	1.0	4	1.0
H	281	5	1.8	2	0.7
I	195	4	2.0	4	2.0
J	294	7	2.4	1	0.3

Table 5
Univariate Analysis of Demographic Characteristics, Clinical Features and Laboratory Values at Time of Each Liver Biopsy with Respect to All Serious Adverse Events and to Bleeding Complications Only

Element	(a) No Complications (n=2677*)		(b) All Serious Adverse Events (n=29)		(c) Bleeding Complication (n=16)		p value	
	Mean/%		Mean/%		Mean/%			
Age at biopsy, yrs	51.8		50.0		54.5		0.21	0.15
Female, %	27.8		44.8		50.0		0.05	0.06
Race, %							0.21	0.21
White, non-Hisp.	72.7		75.9		56.3			
Black/Black + Hisp.	17.6		6.9		12.5			
Hispanic	7.3		10.3		18.8			
Others	2.5		6.9		12.5			
Body Mass Index	29.8		30.2		29.6		0.66	0.93
Tot.Bilirubin mg/dL	0.9		1.0		1.0		0.24	0.27
Albumin g/dL	3.9		3.7		3.6		0.02	0.01
Platelets mm ³	158.3		137.7		120.5		0.12	0.03
Platelets 60,000, %	2.4		18.5		26.7		<0.0001 <0.0001	
INR	1.1		1.1		1.1		0.02	0.11
INR 1.3, %	4.5		18.5		20.0		0.001	0.01
Cirrhosis, %	39.9		44.4		50.0		0.64	0.42
Ishak Fib. Score	4.0		4.3		4.4		0.29	0.23
Specimen length, cm	1.8		1.7		1.7		0.61	0.69
Fragmented, %	18.5		14.3		6.5		0.57	0.22
Ascites on US, %	1.7		4.2		7.1		0.38	0.14
Varices, %**	41.0		90.0		88.9		0.002	0.004
Splenomegaly US, %	36.4		45.5		50.0		0.39	0.35
Fellow biopsy, %	25.3		10.3		12.5		0.07	0.25
> 1 pass, %	64.0		48.3		75.0		0.09	0.37
Cutting needle, %	65.1		55.2		81.3		0.27	0.19

* Excludes 34 patients with adverse events (AE)

**Correlation restricted to second and third biopsies (see text)
Hisp, Hispanic; Tot., total; US, ultrasound

Table 6
Liver Biopsy Bleeding Complication Relative to Platelet Count Cut-Off Values

Platelet Count	Total	Bleeding Complication	
		No.	%
>150,000/mm ³	1331	3	0.2
101,000-150,000/mm ³	738	5	0.7
61,000-100,000/mm ³	509	3	0.6
60,000/mm ³	76	4 *	5.3
Total	2654	15 **	0.6

* Platelet count in 4 patients with bleeding was: 47,000/mm³; 50,000/mm³; 52,000/mm³; and 54,000/mm³.

** One of the 16 patients who bled had neither a platelet count nor an INR at the time of the biopsy

Note: Platelet counts were missing in 40 patients at the time of the visit

Table 7
Liver Bleeding Complication Relative to INR Cut-Off Values

INR	Total	Bleeding Complication	
		No.	%
1.0	1517	6	0.4
1.1	743	3	0.4
1.2	279	3	1.1
1.3	123	3 [*]	2.4
Total	2662	15 ^{**}	0.6

^{*} INR in all three patients who bled was 1.3; platelets count in these patients were: 84,000/mm³; 101,000/mm³ and 115,000/mm³

^{**} One of the 16 patients who bled had neither an INR nor a platelet count at the time of the biopsy

Note: INR values were missing in 32 patients at the time of the visit