A Prospective Study of the Rate of Progression in Compensated, Histologically Advanced Chronic Hepatitis C

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The incidence of liver disease progression among subjects with histologically advanced but compensated chronic hepatitis C is incomplete. The Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial was a randomized study of 3.5 years of maintenance peginterferon treatment on liver disease progression among patients who had not cleared virus on peginterferon and ribavirin therapy. Patients were followed subsequently off therapy. Because maintenance peginterferon treatment did not alter liver disease progression, we analyzed treated and control patients together. Among 1,050 subjects (60% advanced fibrosis, 40% cirrhosis), we determined the rate of progression to cirrhosis over 4 years and of clinical outcomes over 8 years. Among patients with fibrosis, the incidence of cirrhosis was 9.9% per year. Six hundred seventy-nine clinical outcomes occurred among 329 subjects. Initial clinical outcomes occurred more frequently among subjects with cirrhosis (7.5% per year) than subjects with fibrosis (3.3% per year) ($P < 0.0001$). Child-Turcotte-Pugh (CTP) score ≥ 7 was the most common first outcome, followed by hepatocellular carcinoma. Following occurrence of a CTP score ≥ 7, the rate of subsequent events increased to 12.9% per year, including a death rate of 10% per year. Age and sex did not influence outcome rates. Baseline platelet count was a strong predictor of all clinical outcomes. During the 8 years of follow-up, death or liver transplantation occurred among 12.2% of patients with advanced fibrosis and 31.5% of those with cirrhosis. *Conclusion:* Among patients with advanced hepatitis C who failed peginterferon and ribavirin therapy, the rate of liver-related outcomes, including death and liver transplantation, is high, especially once the CTP score reaches at least 7. (HEPATOLOGY 2011;54:396-405)

Most published data on the rate of progression of chronic hepatitis C, except after transfusion-associated non-A, non-B hepatitis,[1] have been derived from single-center studies, which were often small and lacked protocol-driven systematic data collection.[1-10] Based on such reports, the annual incidence of progression to hepatic decompensation in compensated cirrhosis has been estimated to be ≈6% (range, 4%-8%).

Abbreviations: ALT, alanine aminotransferase; CTP, Child-Turcotte-Pugh; HALT-C, Hepatitis C Antiviral Long-term Treatment against Cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model of end-stage liver disease.

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In the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial,[11,12] we enrolled 1,050 patients with histologically advanced chronic hepatitis C who had failed to achieve a sustained virologic response with peginterferon-ribavirin therapy; subjects were assigned randomly to receive low-dose peginterferon alfa-2a (90 μg/week) or no further treatment for 3.5 years.[11] Because the treated and untreated control groups experienced similar rates of clinical progression,[12] the combined HALT-C Trial cohort provided a unique opportunity to determine rates of clinical progression in a large, prospectively followed population with histologically advanced, compensated chronic hepatitis C. Extension of the study beyond the 3.5-year randomized treatment phase for up to 8 years provided the opportunity to characterize prospectively the course of advanced chronic hepatitis C more comprehensively than has been possible heretofore. In this article, we describe the frequency and temporal development of the major clinical outcomes of hepatic decompensation. We also describe the sequential emergence of laboratory changes associated with hepatic dysfunction and their relationship to clinical outcomes.

Patients and Methods

The design of the HALT-C Trial (ClinicalTrials.gov #NCT00006164) and results of this randomized trial of peginterferon maintenance therapy were described.[11,12] To be eligible for the trial, adult patients with chronic hepatitis C had to have failed to achieve a sustained virologic response after a course of at least 12 weeks of interferon-based therapy and have advanced bridging fibrosis (Ishak fibrosis stage 3-4) or cirrhosis (stage 5-6) on a baseline liver biopsy within 12 months prior to enrollment. Potential subjects were excluded for a platelet count $<50{,}000/mm^3$, absolute neutrophil count $<1{,}000/mm^3$, hematocrit level $<33\%$, alpha-fetoprotein level >200 ng/mL, Child-Turcotte-Pugh (CTP) score ≥ 7, or a history of decompensated liver disease or hepatocellular carcinoma (HCC). Patients with other causes of liver disease, uncontrolled comorbid medical (including malignancies, autoimmune disorders, and immunocompromised states) or psychiatric illnesses, or contraindications to interferon were excluded, as were pregnant or breast-feeding women.

Potential participants in the HALT-C Trial were treated in a lead-in phase with peginterferon alfa-2a (180 μg/week subcutaneously) and ribavirin (1,000-1,200 mg/day);[13] those who failed to clear hepatitis C virus (HCV) RNA by week 20, categorized as nonresponders,[11,12] were randomized to 3.5 years of 90 μg/week of peginterferon alfa-2a or to an untreated control group. Subjects with undetectable HCV RNA at treatment week 20 were categorized as responders and received combination treatment for 48 weeks. Responders with detectable HCV RNA after week 20 (breakthrough or relapsers) were also eligible for randomization. In addition, patients failing to achieve a sustained virologic response following peginterferon and ribavirin treatment administered outside the HALT-C Trial were also eligible for randomization. Of 1,730 screened subjects, 1,050 were randomized.[12] Study subjects were seen in one of 10 clinical centers at 3-month intervals through month 48 and every 6 months thereafter until October 2009.

Protocol-defined clinical outcomes included a CTP score of ≥ 7 on two consecutive study visits 3 months apart (6 months apart in the postrandomization phase), variceal hemorrhage, ascites, hepatic

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This is publication #56 of the HALT-C Trial, which has been registered with ClinicalTrials.gov (#NCT00006164).

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encephalopathy, spontaneous bacterial peritonitis, definite HCC, or death either related or unrelated to liver disease. For this analysis we also included liver transplantation and presumed HCC as clinical outcomes. In addition to individual clinical outcomes, we defined three groups of clinical outcome. "Any clinical outcome" was the definition used in the original HALT-C Trial protocol and included death from any cause, presumed or definite HCC, variceal hemorrhage, ascites, spontaneous bacterial peritonitis or hepatic encephalopathy. "Decompensated liver disease" was defined as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy. "HCC/Decompensation" was defined as presumed or definite HCC, as defined,[14] or decompensated liver disease. Protocol biopsies were performed approximately 2 and 4 years after enrollment

The stage of histologic fibrosis was interpreted according to the Ishak score by consensus face-to-face vote of the 10 study-site pathologists and a coordinating pathologist. For subjects in the fibrosis stratum, progression to cirrhosis (Ishak fibrosis stage 5 or 6) was determined. A rotating group of HALT-C Trial investigators, masked as to identity of subject, study site, and randomization group, reviewed every clinical outcome to determine whether it met predefined criteria. In addition, after completion of the study, a mortality committee reviewed every death prior to December 31, 2008, again with masking of subject, site, and randomization group, and classified the death as liver-related or unrelated, based on predefined criteria.[15] For deaths that occurred between January 1, 2009, and October 31, 2009, the clinical site principal investigator determined whether or not the death was liver-related. If the cause was unknown, the death was counted as non–liver-related. Three hundred twenty-nine (31%) patients had an outcome, 197 were followed for $\geq$7 years without an outcome, and 298 were followed for $<$7 years without an outcome but were seen in the last 6 months of the trial, which represented 79% of the study cohort. Analysis of liver transplantation and liver-related death was also included in the current analysis.

Determination of Laboratory Criteria for Disease Progression. Because laboratory data were collected at uniform intervals, we evaluated the rate of progression of laboratory markers of liver disease progression. Prior to analyzing laboratory data, we selected the laboratory thresholds in the CTP score (albumin $\leq$3.5 g/dL, total serum bilirubin $\geq$2.0 mg/dL, international normalized ratio $\geq$1.7), as well as creatinine $\geq$1.2 mg/dL and platelet count $<$100,000/mm^3. We also used a model of end-stage liver disease (MELD) score[16] of $\geq$15.

Statistical Analyses. Statistical analyses were performed at the Data Coordinating Center (New England Research Institutes, Watertown, MA) with SAS (release 9.1) software. Time to outcome was measured as the number of months or years from randomization to the date of the initial clinical outcome. For analyses with the initial events after CTP score $\geq$7, we computed time from the date of the CTP elevation to the date of the initial clinical outcome event after the CTP elevation. For comparison of time to clinical and laboratory outcomes between the fibrosis and cirrhosis strata, we performed Kaplan-Meier life-table analyses and applied the log-rank test. Cox proportional hazards models were used to estimate the relative risks of clinical outcomes. Because outcomes occurred at relatively linear rates, they are reported as annualized rates. Outcomes were counted if they occurred within 8.0 years of randomization and before October 20, 2009. Other than death, clinical outcomes that occurred after liver transplantation were not counted. Annualized rates of cirrhosis development were extrapolated from the 2- and 4-year biopsy results.

The HALT-C Trial was approved by the institutional review boards at each participating site. All patients provided written informed consent before participating in the trial.

Results

In the HALT-C Trial,[12] 1,050 study patients—622 (60%) with noncirrhotic fibrosis (Ishak stages 3-4) and 428 (40%) with cirrhosis (Ishak stages 5-6)—were randomized to maintenance treatment or to an untreated control group for 3.5 years and followed after the randomized phase of the trial for up to an additional 5 years. The median duration of participation in the trial (time from randomization to first outcome or last time known to be outcome-free) was 6.0 years (range, 0-8.7 years). Baseline characteristics of study subjects included mean age 51 years, 71% male, 8.2% African American, estimated mean duration of HCV infection 28 years, and mean body mass index 30 kg/m^2. At baseline, levels of serum alanine aminotransferase (ALT) were elevated in 83% (mean 2.1 $\times$ the upper limit of normal), and mean serum HCV RNA was 6.4 $\log_{10}$ IU/mL. Baseline mean serum total bilirubin (0.8 mg/dL), albumin (3.9 g/dL), and prothrombin time (international normalized ratio, 1.04) were normal.[12] Mean platelet count was 165,000/

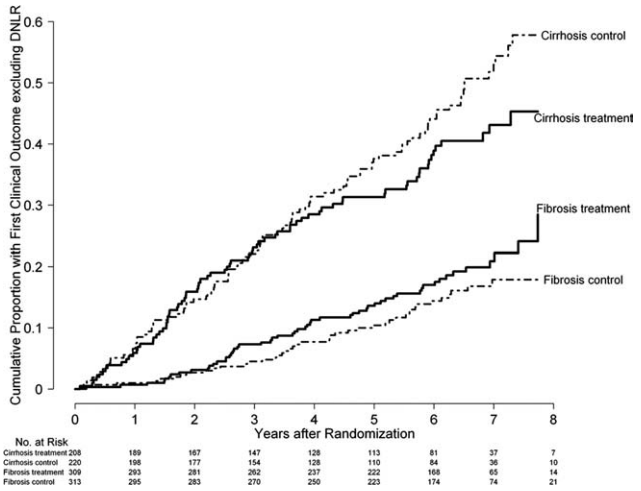

Fig. 1. First clinical outcome rates excluding death not related to liver by stratum and treatment group to year 8.

mm^3; 44.4% of patients had a platelet count $<150{,}000/mm^3$.

Clinical and Histological Outcomes. In the fibrosis stratum, 235 clinical outcomes occurred in 122 patients with an 8-year cumulative incidence of first outcome of 28.8% and annualized rate of 3.6% (Figure 1). In the cirrhosis stratum, 444 clinical outcomes occurred in 207 patients with an 8-year cumulative rate of 60.6% and annualized rate of 7.6% (difference between strata, log-rank test, $P < 0.0001$). Among patients with cirrhosis, the time to first clinical outcome (non–liver-related deaths excluded) occurred at a constant rate throughout the 8-year study period. Among the fibrosis group, first outcomes occurred infrequently during the first year but, thereafter, also occurred at a constant albeit lower rate. Overall, the rate of initial outcomes was similar among patients assigned to peginterferon (5.2% per year) and the control group (5.3% per year, $P = 0.88$); however, the annual rate of initial outcomes was higher in the peginterferon group than in the control group among patients in the fibrosis stratum (4.4% versus 2.9%, $P = 0.04$) and slightly lower in the peginterferon group than in the control group in the cirrhosis stratum (6.6% versus 8.4%, $P = 0.08$). In further analysis of time to first decompensation event (ignoring CTP score $\geq$7), the rate of 1.9% per year among patients assigned to treatment was similar to the rate of 2.5% per year among the control group ($P = 0.16$). Because liver-related outcomes were not markedly influenced by maintenance peginterferon therapy, we combined the peginterferon group and the control group for this analysis. Furthermore, because outcomes occurred at a nearly linear rate over the 8 years of study, we estimated the annual incidence of individual clinical outcomes.

Among the clinical events that constituted outcomes in this analysis, the most frequent first outcome was CTP $\geq$7; followed by HCC (including presumed HCC), death (including those unrelated to liver disease), and ascites (Table 1). During the period of observation, CTP $\geq$7, death (including those unrelated to liver disease), ascites, and HCC were the most common outcomes experienced by patients.

Among patients with baseline fibrosis, 109 progressed to cirrhosis at month 24 and a further 69 had cirrhosis at month 48 (annualized rate of progression to cirrhosis 9.9%) (Table 2). The observed 8-year and calculated annualized incidences of each clinical outcome were three- to four-fold more frequent in the cirrhosis stratum than in the fibrosis stratum (Table 2). Once CTP score rose to $\geq$7, patients with bridging fibrosis at baseline did not differ from those with

Table 1. Frequency of Total Clinical Outcomes and First Outcome, by Stratum

	Fibrosis		Cirrhosis		Total	
Clinical Outcome	Total Number of Outcomes	First Outcome	Total Number of Outcomes	First Outcome	Total Number of Outcomes	First Outcome
All death	49	24	89	29	138	53
Liver-related death	27	5	55	5	82	10
Liver transplantation	30	2	56	2	86	4
Liver-related death or liver transplantation	54	7	103	7	157	14
HCC or presumed HCC	40	35	48	32	88	67
CTP score $\geq$7 on two consecutive visits	49	36	121	101	170	137
Variceal hemorrhage	9	5	18	10	27	15
Ascites	34	12	67	23	101	35
Bacterial peritonitis	6	0	3	0	9	0
Encephalopathy	18	8	42	10	60	18
Total*	235 outcomes	122 patients	444 outcomes	207 patients	679 outcomes	329 patients

Each patient could be counted more than once.

*All-cause death + liver transplantation + HCC or presumed HCC + CTP score $\geq$7 + variceal hemorrhage + ascites + bacterial peritonitis + encephalopathy.

Table 2. Annualized Incidence of Each Clinical Outcome According to Baseline Stage of Fibrosis (Fibrosis or Cirrhosis) and Following CTP Score ≥7

Outcome	Fibrosis Stratum (n = 622)	Cirrhosis Stratum (n = 428)	Events After CTP Score ≥7 (n = 137)
Cirrhosis	9.9%	–	–
CTP score ≥7	1.4%	5.0%	–
Variceal hemorrhage	0.2%	0.9%	1.2 %
Ascites	1.0%	2.9%	12.7%
Encephalopathy	0.5%	1.9%	10.3%
HCC or presumed HCC	1.1%	2.4%	4.5%
All death	1.7%	3.9%	10.0%
All death or liver transplantation	2.2%	5.3%	14.7%
Liver-related death	0.8%	2.6%	8.7%
Liver-related death or liver transplantation	1.6%	4.2%	14.3%
Any clinical outcome (of all deaths, HCC, CTP score ≥7, variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	3.3 %	7.5 %	–
Decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	1.2%	3.9 %	12.9%
HCC/presumed HCC or decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	2.1%	5.5 %	14.8%

cirrhosis at baseline in the rate of subsequent outcomes. Of 137 study patients with CTP score ≥7 as the first clinical outcome, 93 (69%) had a subsequent clinical outcome after a median time of 11 months; liver-related death or liver transplantation was the most frequent event after a CTP score ≥7, followed by clinical decompensation and ascites (Table 2). Demographic features did not influence outcome rates; the annualized incidence of outcomes, including progression to cirrhosis, did not differ between men and women or between patients younger versus older than 50 years ($P > 0.05$) (Table 3). There were too few non-whites or Hispanics to perform meaningful analyses of individual outcomes by ethnic group.

A total of 138 deaths were observed during the study (i.e., through October 20, 2009), 82 (59%) of which were liver-related. After the first 1-2 years of observation, we observed a linear increase in all-cause death and liver-related death for the entire HALT-C Trial population (Figure 2A). The cumulative incidence of all deaths and of liver-related deaths or transplantation was higher among patients who had cirrhosis compared with patients who did not (Figure 2B). Following the development of a CTP score ≥7 (Figure 2C) or a decompensation event (Figure 2D), nearly all deaths were liver-related.

Laboratory Marker Progression and Outcomes. At baseline, the prevalence of hypoalbuminemia, thrombocytopenia, and hyperbilirubinemia was higher among patients with cirrhosis than those without cirrhosis (Figure 3A,B). The cumulative 8-year incidence of abnormal levels was higher in the cirrhosis stratum than the fibrosis stratum for all laboratory markers, except elevated creatinine, which was comparable in both strata (Figure 3A,B). During the observation period, reductions in albumin and in platelet count occurred earlier and more frequently than abnormalities in the other laboratory markers measured.

Low platelet count was shown previously to be the best predictor of overall outcomes in the randomized phase of the HALT-C Trial (through 3.5 years), irrespective of stage of fibrosis.[17] With further observation, we found that the baseline platelet count was

Table 3. Annualized Incidence of Each Clinical Outcome, by Sex and Age

Outcome	Sex		Age	
	Male (n = 745)	Female (n = 305)	<50 Years (n = 532)	≥50 Years (n = 518)
Cirrhosis	9.9%	10.1%	10.5%	9.3%
CTP score ≥7	2.7%	3.3%	3%	2.8%
Variceal hemorrhage	0.5%	0.6%	0.6%	0.4%
Ascites	1.7%	1.8%	1.9%	1.6%
Encephalopathy	1%	1.3%	1.2%	0.9%
HCC or presumed HCC	1.6%	1.5%	1.3%	1.9%
All death	2.4%	2.6%	2%	2.9%
All death or liver transplantation	3.6%	3.3%	3.1%	3.9%
Liver-related death	1.5%	1.5%	1.4%	1.7%
Liver-related death or liver transplantation	2.8%	2.3%	2.4%	2.9%
Any clinical outcome (of all deaths, HCC, CTP score ≥7, variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	4.7%	5.8%	4.7%	5.4%
Decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	2.1%	2.8%	2.5%	2.2%
HCC/presumed HCC or decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	3.3%	3.7%	3.4%	3.6%

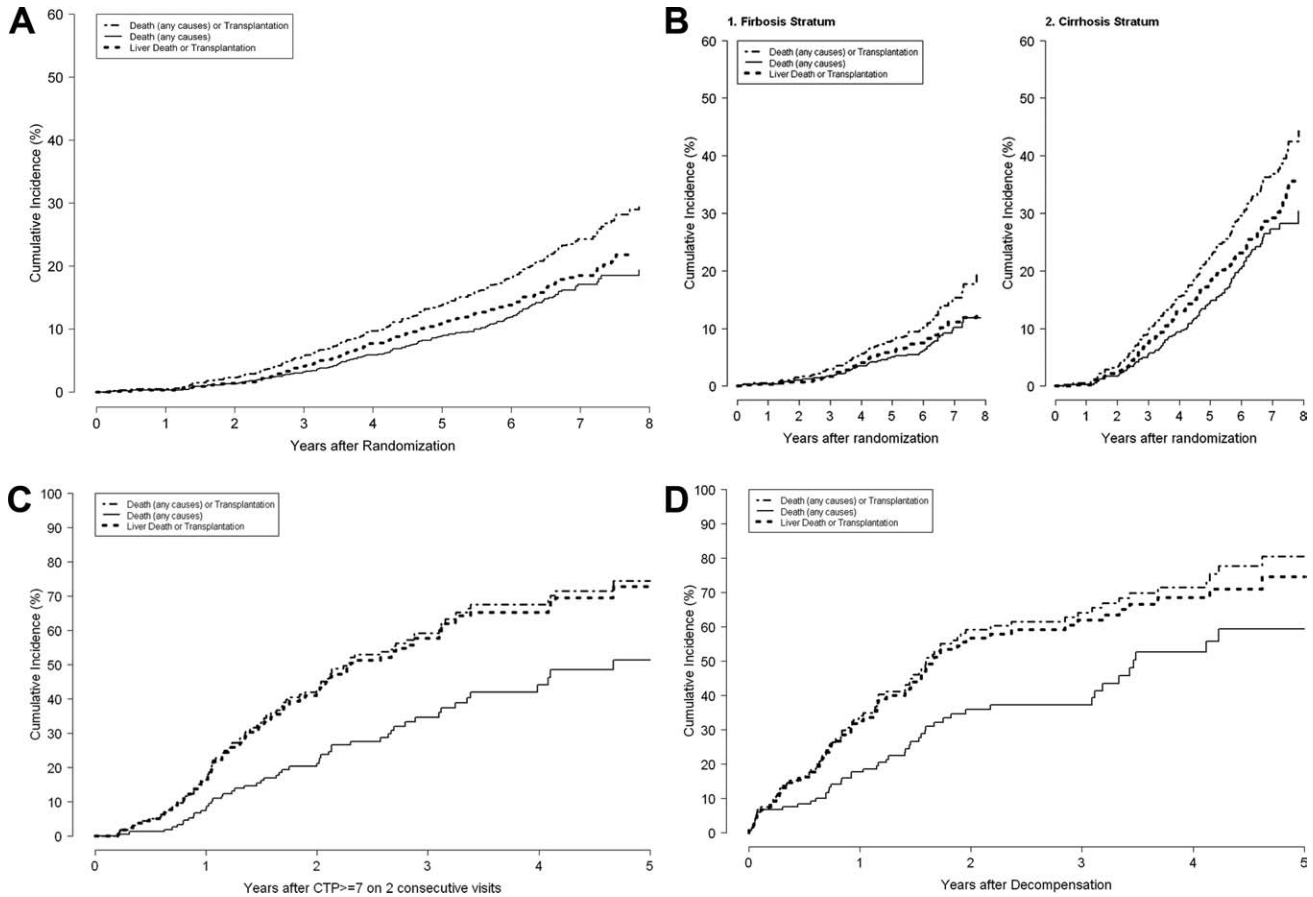

Fig. 2. Cumulative 8-year incidence of all-cause mortality, liver-related mortality and transplantation, and all-cause mortality and liver transplantation. (A) Entire HALT-C Trial population. (B) Noncirrhotic advanced fibrosis and cirrhosis. (C) CTP score $\geq$7 on two consecutive visits. (D) After onset of decompensated liver disease.

associated closely with the annual rate of initial clinical decompensation. The annualized incidence of each clinical outcome increased over decreasing ranges of platelet counts from $\geq$200,000/mm^3 to $<$100,000/mm^3 (Table 4). For example, patients with a platelet count $<$100,000/mm^3 were 11-fold more likely to experience a decompensation event and 14-fold more likely to die a liver-related death or undergo liver transplantation, compared with subjects with a baseline platelet count $\geq$200,000/mm^3.

Rates of outcomes were also evaluated according to baseline body mass index, ALT activity, and serum HCV RNA. The annualized rate of cirrhosis was 8.9% for nonobese subjects versus 11.3% for obese subjects ($P = 0.07$); 8.2% for ALT $<$90 IU/L versus 12.2% for ALT $\geq$90 IU/L ($P = 0.001$); and 11.1% for HCV RNA $<$6.5 $\log_{10}$ IU/mL versus 9.0% for HCV RNA $\geq$6.5 $\log_{10}$ IU/mL ($P = 0.046$). Rate of any clinical outcome was not associated with baseline obesity or with ALT activity ($P \geq 0.30$) but was associated with lower HCV RNA level ($P < 0.0001$). The association of outcomes with HCV RNA level was not adjusted for stage of fibrosis, which was strongly and inversely associated with HCV RNA level ($P < 0.0001$).

Discussion

Understanding the natural history of advanced hepatitis C has been challenging. Limitations in study design or execution of most, if not all, prior studies could have led to inaccurate results. No prior study had the rigor of the histological evaluation of the HALT-C Trial, in which three liver biopsies were performed and each biopsy was assessed by a team of 11 expert liver histopathologists who were masked to all patient information.[11,12] Additionally, few if any prior studies had uniform monitoring of patients at regular intervals and predefined case definitions, whereas patients in the HALT-C Trial were evaluated every 3-6 months throughout the study, and all outcomes were reviewed independently by experienced hepatologists. Furthermore, all patients in the HALT-C Trial had failed to clear HCV during peginterferon and ribavirin

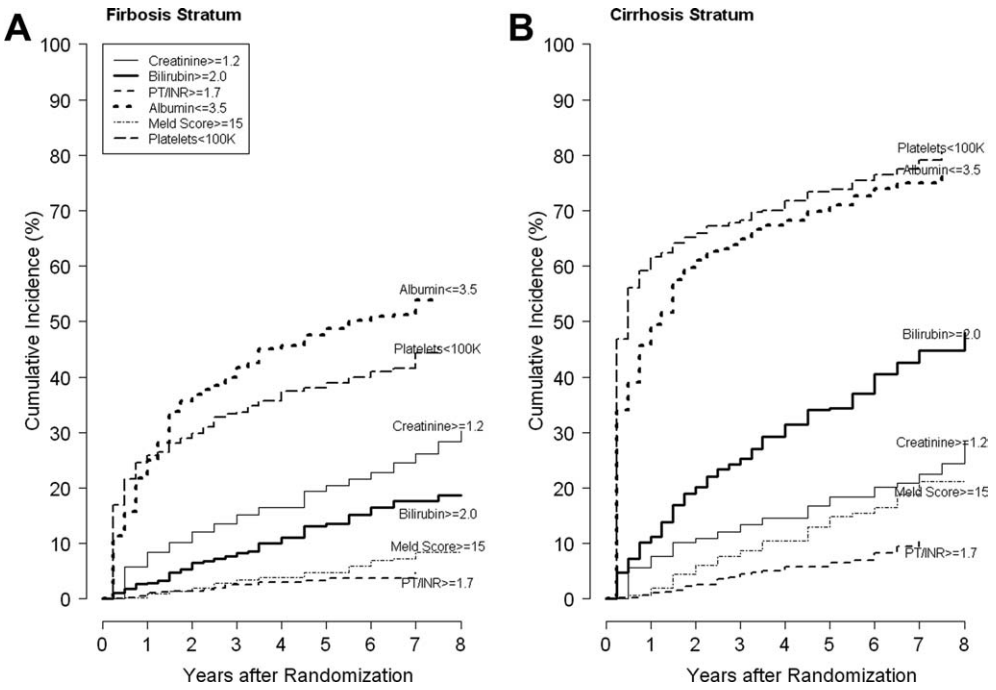

Fig. 3. Cumulative incidence of laboratory abnormalities over time in (A) the fibrosis stratum and (B) the cirrhosis stratum.

therapy, whereas in several other studies, progression was evaluated in patient cohorts, only subsets of whom were treated, and in whom selection for therapy was not based on uniform criteria.

For the HALT-C Trial, our hypothesis was that 3.5 years of maintenance, low-dose (90 μg/week) peginterferon therapy would retard the progression of chronic hepatitis C in patients with advanced fibrosis; unfortunately, maintenance therapy was found to be ineffective. Because clinical outcome rates were either indistinguishable between treated and control patients or were inconsistently different (higher mortality among treated patients with noncirrhotic fibrosis and lower incidence of HCC among treated patients with cirrhosis), we pooled the two groups for an analysis of the rate of progression of chronic hepatitis C. We followed the combined cohort of >1,000 patients with clinically compensated advanced fibrosis or cirrhosis, both during the randomized (maintenance versus control) phase and the postrandomization phase for up to 8 years (median, 5.6 years). Thus, this is the single largest prospective study of clinical and laboratory progression among patients with chronic hepatitis C and advanced fibrosis; one of the longest followed cohorts; and the

Table 4. Annualized Incidence of Each Clinical Outcome, According to Baseline Platelet Count

Outcome	Platelet Count at Baseline Visit				
	<100 (n = 188)	100 to <150 (n = 278)	150 to <200 (n = 282)	≥200 (n = 276)	All (n = 1,024)
CTP score ≥7	7.6%	3.4%	1.5%	0.6%	2.9%
Variceal hemorrhage	1.3%	0.4%	0.2%	0.2%	0.5%
Ascites	4.8%	2.2%	0.9%	0.5%	1.8%
Encephalopathy	2.6%	1.3%	0.4%	0.1%	1.0%
HCC or presumed HCC	3.6%	1.9%	1.0%	0.5%	1.6%
All death	5.3%	2.6%	1.9%	1.0%	2.4%
All death or liver transplantation	7.3%	4.0%	2.4%	1.1%	3.4%
Liver-related death	4.3%	1.2%	1.3%	0.3%	1.5%
Liver-related death or liver transplantation	6.4%	2.9%	1.8%	0.5%	2.6%
Any clinical outcome (of all deaths, HCC, CTP score ≥7, variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	10.2%	6.1%	3.2%	2.1%	5.0%
Decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	6.0%	2.8%	1.1%	0.5%	2.3%
HCC/presumed HCC or decompensation (variceal hemorrhage, ascites, bacterial peritonitis, encephalopathy)	7.9%	4.1%	2.0%	1.3%	3.5%

Twenty-six patients with prior splenectomy were excluded.

only sizable study of an American cohort, most previous reports having focused on European and Japanese populations.[2,6-9,18]

We present the incident rates of clinically meaningful outcomes for patients at three stages of advanced liver disease: advanced noncirrhotic fibrosis, compensated cirrhosis, and decompensated cirrhosis (CTP score $\geq$7). The observed annual rates of all-cause mortality and liver transplantation were 2.2% in patients with noncirrhotic fibrosis and 5.3% in those with cirrhosis, similar to rates reported in European and Japanese studies. As anticipated, the rate of clinical outcomes (especially CTP score elevation and variceal hemorrhage) was higher among patients with cirrhosis at baseline than those with noncirrhotic fibrosis. Among patients with noncirrhotic fibrosis, the annual incidence of initial clinical outcomes ranged from 0.25% per year for variceal hemorrhage to 1.4% per year for CTP elevation; of note, these outcomes of end-stage liver disease (including HCC and liver-related death) occurred in the absence of documented cirrhosis at entry into the HALT-C Trial, although we cannot exclude the possibility that some patients may have been understaged at entry or progressed to cirrhosis by the time an outcome developed. For patients with histological cirrhosis at entry into the HALT-C Trial, the annual incidence of clinical outcomes ranged from 0.9% per year for variceal hemorrhage to 5.0% per year for CTP score elevation. Among individual clinical outcomes, the most frequent initial decompensation event was an increase in CTP score to $\geq$7. Once the CTP score became elevated, the incidence of second clinical events was indistinguishable between subjects in the fibrosis and cirrhosis strata. Thereafter, morbidity and mortality rates increased substantially, confirming the value of a rise in CTP score as an ominous prognostic sign.

Findings among HALT-C Trial patients with noncirrhotic fibrosis and cirrhosis can be compared with estimates drawn from other studies. Based on the readings from three liver biopsies over $\approx$4 years, HALT-C Trial patients with bridging fibrosis had an annual incidence of cirrhosis of 9.9% per year, a rate that differed little with sex or age and that was comparable to an estimated annual incidence of 11.5% derived from a meta-analysis conducted in 2007.[19] Our directly observed, empirical results differ from those in a recent modeling projection in which an approximate four-fold difference in progression to cirrhosis was assumed between younger women and older men.[20] A potential explanation for the lack of an effect of sex and age on disease progression in our study may be that once advanced liver disease has developed, age and sex may no longer influence disease progression. In a recent systematic overview of outcomes among patients with HCV-related compensated cirrhosis, information was summarized from 13 cohort studies: eight from Western Europe, four from Japan, and one from the United States.[21] The 5.3% per year rate of death or transplantation in patients with cirrhosis from the current study is well within the reported range of 2.7%-6.7%, and the 2.4% per year rate of HCC is at the lower end of the reported range of 1.8%-7.1%. For HCC, the highest reported rates came from Japan.

In addition to studying the occurrence of clinical events, we monitored the development of laboratory abnormalities that are associated with deteriorating liver function. Hypoalbuminemia and thrombocytopenia were common at study entry, but their occurrence rates and those of other laboratory abnormalities were relatively linear over the 8 years of observation. The MELD score, which is based on serum bilirubin, creatinine, and international normalized ratio/prothrombin time, determines priority for liver transplantation in the United States, with a minimum score of 15 for a patient to be considered for transplantation. Among patients with fibrosis, the rate of development of a MELD score $\geq$15 was low; the 8-year cumulative incidence was $\approx$8%. Among patients with cirrhosis, the 8-year cumulative incidence was higher ($\approx$21%). These calculations do not include the MELD score upgrade for patients with HCC, who constituted nearly half of the patients in the HALT-C Trial cohort who underwent transplantation. We demonstrated previously that thrombocytopenia was a strong predictor of progressive liver disease,[17] which was confirmed in this analysis with longer follow-up. Outcome rates varied many fold with progressively lower platelet counts (Table 4). Given the high rate of clinical events among patients with thrombocytopenia, it is particularly concerning that thrombocytopenia developed among $\approx$40% of patients with fibrosis and 80% of patients with cirrhosis during the 8 years of observation (Figure 3). Such information could be especially useful in predicting prognosis in the absence of liver biopsy.

The major strength of this report is that it represents the largest prospective study of the progression of chronic hepatitis C and one of the only such studies conducted in the United States. Although derived from a large, multicenter study, these results would not necessarily apply to all patients with advanced hepatitis C. Study patients had to meet the stringent inclusion and exclusion criteria for the clinical trial. They could not have other causes for liver diseases,

they were not injection drug users or excessive alcohol consumers at the time of enrollment, they demonstrated the motivation and ability to tolerate long-term peginterferon therapy, and they had failed to clear HCV on standard doses of peginterferon and ribavirin. Although patients in the HALT-C Trial might be a nonrepresentative sample of current patients with HCV infection and histologically advanced liver disease, they are fairly representative of the types of patients clinicians will encounter increasingly. With the wide availability and application of antiviral therapy, many patients with advanced fibrosis who will be monitored clinically are those who have already failed a course of antiviral therapy and who do not have good treatment options for prevention of liver disease progression. In an era of antiviral therapy, studies of the true, intervention-free natural history of chronic hepatitis C can no longer be performed, and our data, reflective of a more relevant patient demographic, will provide clinical guidance most applicable to the emerging patient population.

The other strengths of this report are the rigor of data collection and the breadth of the predefined outcomes. All patients met clearly defined enrollment criteria, including a biopsy that demonstrated histologically advanced liver disease and that excluded other causes of severe disease. We are not aware of reports of other patient populations in which the progression of disease was documented for the three groups of patients included in the current study: those with precirrhotic fibrosis, compensated cirrhosis, and early decompensated liver disease. Serial liver biopsies were obtained from the large majority of patients and read centrally by expert histopathologists. Patients attended protocol-driven, regularly scheduled appointments, during which the presence and absence of each clinical outcome was determined. Finally, all clinical outcomes were confirmed by an independent panel of study hepatologists.

In conclusion, we have documented the rate of development of histologically defined cirrhosis in patients with chronic hepatitis C and advanced fibrosis as well as the incidence of clinically meaningful outcomes among patients with noncirrhotic fibrosis, cirrhosis, and early decompensated liver disease. Moreover, we demonstrated the rates at which laboratory abnormalities developed as well as the relationship of platelet count to outcome rate. Such data should be helpful in guiding physicians who follow patients with histologically advanced chronic hepatitis C, preparing them for what outcomes to anticipate and at what annual incidence.

Appendix

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