Quantitative Tests of Liver Function Measure Hepatic Improvement after Sustained Virologic Response: Results from the HALT-C Trial

Gregory T. Everson, Mitchell L. Shiffman, John C. Hoefs, Timothy R. Morgan, Richard K. Sterling, David A. Wagner, Jennifer L. DeSanto, Teresa M. Curto, Elizabeth C. Wright, and the HALT-C Trial Group.

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BACKGROUND

More than 2.7 million Americans are infected with the hepatitis C virus, 8,000 to 10,000 die annually due to complications of chronic hepatitis C, and the number of Americans infected for 20 or more years will not peak until 2015 (1-4). As a consequence, the number of patients who will decompensate, advance to hepatocellular carcinoma, and need liver transplantation will increase (5-10).

Rates of sustained virologic response (SVR) with peginterferon/ribavirin treatment of chronic hepatitis C (11-14) are lower in patients with advanced hepatic fibrosis or cirrhosis (15-17). In the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial, patients with chronic hepatitis C with bridging fibrosis or compensated cirrhosis (Child-Turcotte-Pugh ≤6) and prior nonresponse were retreated with peginterferon/ribavirin (18). In this cohort, SVR after retreatment declined stepwise, from 23% to 9%, with increasing severity of disease, as defined by liver histology and platelet count (15). Because quantitative tests of liver function (QLFTs) measure the continuum of liver impairment, we reasoned that the relationship between SVR and disease severity might be better defined by QLFTs.

SVR reduces hepatic inflammation, fibrosis (19,20), and rates of clinical outcomes (21-25). The principal clinical manifestations of advanced chronic hepatitis C, such as varices, ascites, and encephalopathy, are linked to portal hypertension and impaired hepatic function. Beneficial effects of SVR on hepatic fibrosis and clinical outcomes are likely mediated through improvements in the portal circulation and hepatic function – improvements which could be detected by QLFTs but not by standard laboratory tests. In this study of retreatment of patients with chronic hepatitis C with peginterferon/ribavirin, we utilized a battery of QLFTs to measure hepatic metabolism, hepatic and portal blood flow, portal-systemic shunting, and hepatic parenchymal mass. One goal was to define the relationships between severity of hepatic impairment, as measured by QLFTs, and virologic responses. In addition, we used serial QLFTs to define hepatic improvement after achievement of sustained virologic response.

METHODS

Participants (N=232) were enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial, had failed prior therapy, had bridging fibrosis or cirrhosis, and were retreated with PEG/RBV. All 232 patients had baseline QLFTs; 24 patients with SVR and 68 nonresponders had serial QLFTs. Lidocaine, [24-13C]cholate, galactose, and 99mTc-sulfur colloid were administered intravenously; [2,2,4,2-2H]cholate, [1-13C]methionine, caffeine, and antipyrine were administered orally. Clearances (Cl), breath 13CO2, monoethylglycylxylidide (MEGX), perfused hepatic mass (PHM), and liver volume were measured.

RESULTS

Rates of SVR were 18 to 26% in patients with good function by QLFTs but <6% in patients with poor function. Hepatic metabolism, measured by caffeine kelim (P=0.02), antipyrine kelim (P=0.05), and antipyrine Cl (P=0.02), and the portal circulation, measured by cholate Cloral (P=0.0002) and cholate shunt (P=0.0003), and PHM (P=0.03), improved after SVR.

Boundaries for Quartiles of Quantitative Tests of Liver Function

	Best Function	25th Percentile	50th Percentile	75th Percentile	Worst Function
Tests of Metabolism					
Caffeine k_{elim} (h^{-1})	0.28	0.09	0.06	0.04	0.01
Antipyrine k_{elim} (h^{-1})	0.09	0.04	0.03	0.03	0.01
Antipyrine Cl (ml/min)	79	39	29	21	12
$MEGX_{15min}$ (ng/ml)	70	25	16	8	0
$MEGX_{30min}$ (ng/ml)	98	30	20	13	1
MBT	308	84	65	45	6
Tests of Total Hepatic Blood Flow					
Cholate k_{elim} (min^{-1})	0.27	0.11	0.09	0.08	0.02
Cholate Cl_{iv} (ml/min)	903	459	367	305	155
GEC (mg/kg·min)	10.1	5.6	4.7	4.0	2.1
Tests of Portal Circulation					
Cholate Cl_{oral} (ml/min)	3036	1463	1113	771	255
Cholate Shunt (%)	10	27	36	48	91
Tests of Hepatic Parenchyma					
Perfused Hepatic Mass	114	105	100	94	70
Liver Volume (ml)	2690	1867	1593	1343	769

CONCLUSIONS

Hepatic dysfunction impairs the virologic response to PEG/RBV. SVR improves hepatic metabolism, the portal circulation, and perfused hepatic mass.