The spectrum of hepatic functional impairment in compensated chronic hepatitis C: Results from the HALT-C Trial

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BACKGROUND

In routine clinical practice, chronic hepatitis C (CHC) is monitored by history and physical examination, standard blood testing, ultrasonography and liver biopsy. Goals of monitoring include definition of disease severity, assessment for progression and evaluation of the impact of treatments or interventions. Patients with late stages of disease are identified by deterioration in laboratory tests and development of clinical complications, but patients with earlier stages of disease have stable laboratory tests and no clinical findings despite hepatic functional impairment and portal hypertension. Prior to laboratory or clinical deterioration, the progression of CHC from fibrosis to cirrhosis disrupts hepatocyte function, distorts the hepatic architecture, and alters hepatic and portal blood flow. Therefore, tests measuring hepatic function, blood flow or mass might better define the spectrum of hepatic impairment in fibrotic stages of CHC prior to obvious laboratory or clinical deterioration.

Hepatic metabolism, blood flow, portal-systemic shunt and perfused mass can be defined by administration of test compounds and measuring clearance or quantifying metabolites. These tests are collectively categorized as quantitative liver function tests (QLFTs). Clearances of certain compounds, such as aminopyrine, antipyrine, caffeine, erythromycin and formation of monoethylglycine xylidide (MEGX) from lidocaine, assess hepatic metabolism. In contrast, clearances of others, such as bile acids, lidocaine, propranolol, nitroglycerin and indocyaninine green, assess hepatic or portal blood flow. Simultaneous measurement of clearances of orally and intravenously administered cholate assesses portal-systemic shunting (cholate shunt). Hepatic uptake of intravenously administered 99mTechnetium (99Tcm) sulphur colloid, measured by Single Photon Emission liver-spleen scan (SPECT-LSS), defines perfused hepatic mass (PHM).

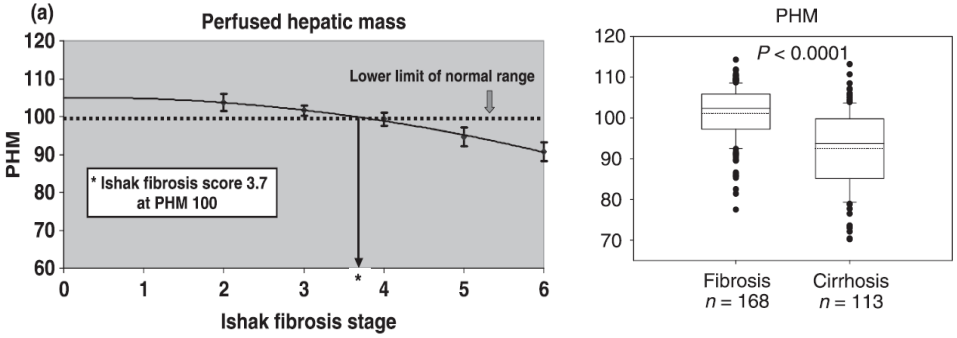
The primary goal of our study was to define the severity of hepatic impairment in a cohort of patients with CHC who had fibrosis, including cirrhosis, but who lacked biochemical or clinical decompensation. In this study, we defined hepatic impairment from a battery of QLFTs. This battery assessed hepatic metabolic capacity, hepatic blood flow, portal blood flow, portalsystemic shunt and PHM.

METHODS

We studied 285 adult patients with chronic hepatitis C prior to treatment in the Hepatitis C Anti-viral Long-term Treatment against Cirrhosis Trial; 171 had Ishak fibrosis stages 2–4 (fibrosis) and 114 had stage 5 or 6 (cirrhosis). None had had clinical decompensation. A battery of 12 quantitative liver function test assessed the spectrum of hepatic microsomal, mitochondrial and cytosolic functions, and hepatic and portal blood flow.

RESULTS

Twenty-six to 63% of patients with fibrosis and 45–89% with cirrhosis had hepatic impairment by quantitative liver function test; patients with cirrhosis had the greatest impairment (P-value ranging from 0.15 to <0.0001). Cholate Cloral, cholate shunt and perfused hepatic mass correlated with cirrhosis, stage of fibrosis (r =)0.51, +0.49,)0.51), varices and variceal size (r =)0.39, +0.36,)0.41). PHM < 95 and cholate shunt >35% identified 91% of patients with medium- or large-sized varices.



CONCLUSIONS

Hepatic impairment is common in compensated patients with fibrosis or cirrhosis because of chronic hepatitis C. Cholate shunt, and cholate Cloral and perfused hepatic mass, identify patients at risk for cirrhosis or varices.

Despite the stable, compensated characteristics of our study population, we discovered significant hepatic impairment in a high percentage of patients – a finding that was not appreciated by standard laboratory tests. Not surprisingly, QLFTs were worse in patients with cirrhosis and the degree of hepatic impairment measured by QLFTs correlated with Ishak stage of fibrosis. Our results are novel because they represent the first description of these relationships using a broad array of QLFTs in a group of patients without clinical or biochemical decompensation. Thus, functional assessment by QLFTs at earlier stages of disease may be more sensitive than standard clinical assessment in identifying those patients with hepatic impairment – patients who may be most at risk for future clinical decompensation.