Changes in Liver Volume in Patients with Chronic Hepatitis C Undergoing Antiviral Therapy

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Aim: **Liver volumetric analysis has not been used to detect hepatic remodelling during antiviral therapy before. We measured liver volume (LV) changes on volumetric magnetic resonance imaging during hepatitis C antiviral therapy.** ***Methods:*** **22 biopsy-staged patients (median [range] age 45^{19-65} years; 9F, 13M) with chronic hepatitis C virus infection were studied. LV was measured at the beginning, end of treatment and 6 months post-treatment using 3D T_1-weighted acquisition, normalised to patient weight. Liver outlines were drawn manually on 4 mm thick image slices and LV calculated. Inter-observer agreement was analysed. Patients were also assessed longitudinally using biochemical parameters and liver stiffness using Fibroscan™.** ***Results:*** **Sustained viral response (SVR) was achieved in 13 patients with a mean baseline LV/kg of 0.022 (SD 0.004) L/kg. At the end of treatment, the mean LV/kg was 0.025 (SD 0.004, $P = 0.024$ *cf* baseline LV/kg) and 0.026 (SD 0.004, $P = 0.008$ *cf* baseline LV/kg) 6 months post-treatment ($P = 0.030$ *cf* baseline, $P = 0.004$). Body weight-corrected end of treatment LV change was significantly higher in patients with SVR compared to patients not attaining SVR ($P = 0.050$). End of treatment LV change was correlated to initial ALT ($R^2 = 0.479$, $P = 0.037$), but not APRI, AST, viral load or liver stiffness measurements. There was a correlation of 0.89 between observers for measured slice thickness.** ***Conclusions:*** **LV increased during anti-viral treatment, while the body weight-corrected LV increase persisted post-antiviral therapy and was larger in patients with SVR. (J Clin Exp Hepatol 2016;6:15–20)**

Hepatitis C virus (HCV) is a blood-borne hepatotrophic RNA virus of significant worldwide public health concern.[1] Currently estimates indicate that there are 270–300 million people infected worldwide with the incidence of HCV expecting to peak in the next 10–20 years.[1] Treatment of HCV aims to improve outcome by slowing or halting progression to cirrhosis and hepatocellular carcinoma (HCC), but serial biopsy during or following treatment is not considered necessary or ethical at present. Non-invasive methods of assessing pathological changes in the liver are being assessed, but are often expensive, conceptually difficult or require specialist equipment.[2] At present, there is no accepted physiological description of any remodelling changes occurring during antiviral therapy, nor is there an accepted proxy to virological measurement to assess response to treatment.

Patients with chronic liver disease (CLD) frequently undergo imaging studies using magnetic resonance imaging (MRI) scanning primarily for the assessment of focal lesions. Volumetric analysis of the liver by MRI[3,4] is applicable to many clinical settings.[5–7] In operative planning particularly for partial hepatectomy prior to surgery[3] for malignancy and for live-related liver donation, liver volume (LV) is useful in assessing the risk of inducing liver failure in the resection candidate[8] or ''small-for-size'' syndrome in the graft recipient.[9] Smaller LVs are seen in more advanced cases of fibrosis and in increasing Child–Pugh class of cirrhosis.[10] In patients with cirrhosis and portal hypertension, a LV of 75% can be expected, compared to age-matched controls. LV may also be related to pre-fibrotic metabolic processes such as steatosis or hepatitis B.[11] Patients with non-alcoholic fatty liver disease (NAFLD) have increased LV which has been shown to decrease on intensive weight loss programs.[12] Furthermore, NAFLD is associated with faster disease progression in HCV and may contribute to the baseline LV prior to treatment. Some authors have suggested that it is useful to assess changes in volume over time as an indicator of therapeutic effectiveness and or disease progression.[13]

Keywords: hepatitis C virus, liver volume, magnetic resonance imaging, sustained viral response
Received: 10.10.2015; *Accepted:* 27.11.2015; *Available online:* 6 December 2015
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Abbreviations: ALT: Alanine aminotransferase; APRI: Aspartate transaminase to platelet ratio index; AST: Aspartate transaminase; CHC: Chronic hepatitis C; CLD: Chronic liver disease; CT: Computed tomography; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; LV: Liver volume; MRI: Magnetic resonance imaging; NAFLD: Non-alcoholic fatty liver disease; NI: Necroinflammatory; SVR: Sustained viral response
http://dx.doi.org/10.1016/j.jceh.2015.11.004

Hepatitis C

MRI is well established as an accurate means to measure LV.[4,14] Unlike computed tomography (CT) scanning, MRI avoids the subject being exposed to ionising radiation, and the use of nephrotoxic contrast media is not necessary for volumetric analysis. CT volumetry has been employed in LV estimation in patients with acute liver failure,[5,15] although this is likely due to a pragmatic choice of rapid scanning modality in these critically ill patients. Longitudinal measurement of LV during treatment for chronic HCV infection has never been performed previously, and MR would be a preferred platform to perform this readily understood and exportable potential longitudinal marker.

The purpose of this study was to measure and observe any changes in LV accurately in a cohort of patients undergoing therapy for chronic hepatitis C infection with pegylated interferon-alpha and ribavirin and assess the correlation of volumetric change with biochemical, virological and ultrasound transient elastography (Fibroscan™, Echosens, Paris, France) indices of treatment response to help understand putative hepatic remodelling processes during successful viral eradication.

METHODS

Patient Selection

Twenty-two patients with chronic hepatitis C (CHC) were prospectively recruited over a 2-year period from Imperial College Healthcare Trust with prior informed, written consent obtained from each subject. Ethical approval was obtained from the regional ethics committee in accordance with the 1975 Declaration of Helsinki, (ethics reference no. 06/Q041/10). Patients were studied at the beginning and 6 months after stopping treatment with pegylated interferon alpha 2a and ribavirin, the treatment time being genotype dependent with 24 weeks treatment given for genotypes 2 and 3, while genotypes 1 and 4 received 48 weeks treatment. Patients were included if they were aged 18–65 years, had evidence of replicating HCV infection on HCV RNA testing (Abbott Realtime HCV assay, Abbott Diagnostics, Illinois, USA), and had been referred for percutaneous liver biopsy for clinical indications. Patients were excluded if they consumed >20 g of alcohol per day; were obese (with a body mass index >30 kg/m^2) or diabetic; if they were taking antiviral therapy; were co-infected with HIV or hepatitis B; were currently taking intravenous drugs, antihypertensive or lipid-lowering medications; had ongoing illness or had evidence of hepatic decompensation. Histological grading was performed by an experienced histopathologist using standardised scoring criteria. Sustained virological response (SVR) was defined as no detectable virus on quantitative RNA testing 6 months post-treatment. Length of treatment was decided by genotype as per European Association for the Study of the Liver (EASL) guidelines.[16] All patients completed the study.

MRI

Patients were scanned using a Philips 1.5 T Achieva™ MRI (Philips Medical Systems, Best, Netherlands). Scans were performed at baseline, 3 months, end of treatment and 6 months post-treatment. Using a SENSE surface body coil, TFE 3D T_1-weighted DRIVe Equilibrium sequence were performed in a single breath-hold following hyperventilation. The parameters were FOV 375 × 260, TR 7, TE 3.4, FA 15, 50 slices 8 mm/4 mm, thus resulting in 4 mm slice thickness. All the data were sent to one workstation (Viewforum version R4.2V1L2 [Philips Medical Systems, Best, The Netherlands]. The edge of the liver contour was manually drawn using the curser by an observer with 14 years' experience in MR imaging (JAF). This process was repeated for each slice; approximately 50 per examination, a total of 3500 contours were drawn in total (Figure 1). The ViewForum gives an area in mm,^{2} which was then multiplied by 4 to obtain a volume for the slice. These values were summed and divided by 1,000,000 to obtain a volume in litres. The LV was normalised to patient weight given the expected change in weight during antiviral therapy.

An exercise in reproducibility was also undertaken for LV. Two observers (one experienced radiographer (JAF) and one hepatologist (AZ) analysed 46 randomised slices five times, over a disparate timeframe resulting in 230 liver areas being analysed. Further comparison was made by measuring and comparing the two observers drawing contours five times around five slices.

Non-invasive Markers of Liver Fibrosis

On the same day as MRI volume studies, all patients had serial standard blood liver biochemistry and both serum Enhanced Liver Fibrosis test (ELF™) (Siemens Healthcare Global, Erlangen, Germany) and hepatic liver stiffness measurements using Fibroscan™ (Echosens, Paris, France) as non-invasive markers of liver fibrosis.

Statistical Methods

Variables pre- and post-treatment were compared using paired *t*-testing and repeated measures ANOVA and % change in these variables was also assessed using one-way ANOVA. Coefficients of variability among measurements for the same patient were estimated and variability among observers was assessed using the intra-class correlation coefficient (ICC). Statistical significance was defined at the 95% level and all *P*-values calculated were two-tailed. Normality was assessed using the D'Agostino-Pearson test. Statistical analysis was performed using SPSS v 15 (SPSS, Chicago, USA) and MedCalc v 11.1 (MedCalc, Mariakerke, Belgium).