Estimation of the Prevalence of Liver Fibrosis in Patients Receiving Chronic Methotrexate Therapy With MR Elastography

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Introductions: Methotrexate (MTX) has become the most frequently prescribed disease modifying antirheumatic agent (DMARD) for rheumatoid arthritis (RA) [1], due to its efficacy, low cost and tolerability. An ongoing primary concern of MTX treatment is its potential hepatotoxicity. Guidelines published in 1994 by the American College of Rheumatology (ACR) suggest that serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin be monitored every 4-8 weeks for assessing hepatotoxicity in RA patients receiving MTX [2]. If a patient develops 5 of 9 abnormal AST values within a 12 month time frame or if serum albumin decreases below the normal range, a liver biopsy is recommended. Although it is invasive and expensive, liver biopsy is currently the gold standard of detecting hepatic fibrosis. Aggregate data from several studies reported in the guidelines showed that 103/719 (14%) and 6/719 (0.89%) of RA patients receiving MTX had mild (grade IIIA) and moderate (grade IIIB) fibrosis on liver biopsy findings, respectively; 2/719 (0.28%) had grade IV cirrhosis [2]. Most of these patients were treated on average for less than 5 years. Because of the apparently low rate of clinically significance, MTX related hepatotoxicity, the usefulness and cost-effectiveness of such frequent monitoring, particularly in the absence of risk factors for liver disease have been brought into question. On the other hand, early studies of MTX related hepatotoxicity often attributed liver fibrosis to MTX without full consideration of confounding factors, particularly with respect to non-alcoholic steatohepatitis (NASH) [3], a disease which often results in liver fibrosis and cirrhosis. Uncertainty also exists about whether the risk for liver fibrosis is increased with cumulative doses of MTX. Some studies have determined a dose related effect of liver fibrosis with MTX [4, 5]; others, however, have not [6, 7].

The unavailability of accurate non-invasive hepatic fibrosis detection methods other than biopsy has frustrated clinicians in addressing these important questions. Since its advent 15 years ago [8], Magnetic Resonance Elastography (MRE) has developed into a clinical-ready-to-use diagnostic technology whose high diagnostic accuracy for in vivo human liver fibrosis has been exploited in a number of ways [9-12]. Our previous study of 85 subjects showed that, with a cut-off value of 2.93 kPa, the predicted sensitivity and specificity of MRE for detecting all grades of liver fibrosis is 98% and 99%, respectively [11]. This abstract reports interim results from a currently ongoing project using MRE to assess hepatic fibrosis in RA patients who are on MTX treatment seen at our institution.

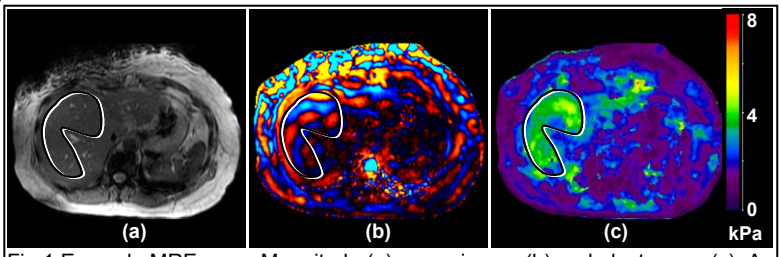

Fig.1 Example MRE scan: Magnitude (a), wave image (b) and elastogram (c). An ROI was drawn on the elastogram where wave SNR is high, excluding large blood vessels and severe wave interferences; hepatic stiffness of this patient: 3.36±0.23 kPa.

Methods and Materials: After Institutional Review Board (IRB) approval and obtaining informed consent, 49 RA patients (13 males, 36 females) currently on MTX treatment underwent MRE scanning. Patient age range was 27 to 81 years (mean: 62); body mass index ranged from 19.6 to 49.9 (mean: 28.7). Exclusion criteria included: 1. patients with established causes of chronic liver disease (hepatitis B or C, hemato-chromatosis and alpha-antitrypsin deficiency); 2. patients with contraindications to MR examination (MR safety, claustrophobia); 3. pregnancy. The hepatic MRE technique used here was described in a previous publication [11]. The MRE parameters used here included: MR scanner=1.5 T (GE, Wisconsin, USA); sequence= GREMRE; mechanical frequency=60Hz; phase offsets = 4; MENC = 32μm/radian; imaging plane=axial; motion sensitizing direction= axial; FOV=32-44cm; matrix =256X96; fractional phase FOV=0.75-1; flip angle= 30°; NEX=1; Bandwidth =31.25 kHz; TE/TR=24.5/50 msec; slice thickness=10mm; number of slices=2; slice position = close to largest hepatic cross-section area; patient position=supine; scan time=4 breath-holds (17 sec). Region of interest (ROI) was drawn on the liver region of the elastogram where wave SNR is high, avoiding large blood vessels found in the magnitude image and severe wave interferences found in wave images.

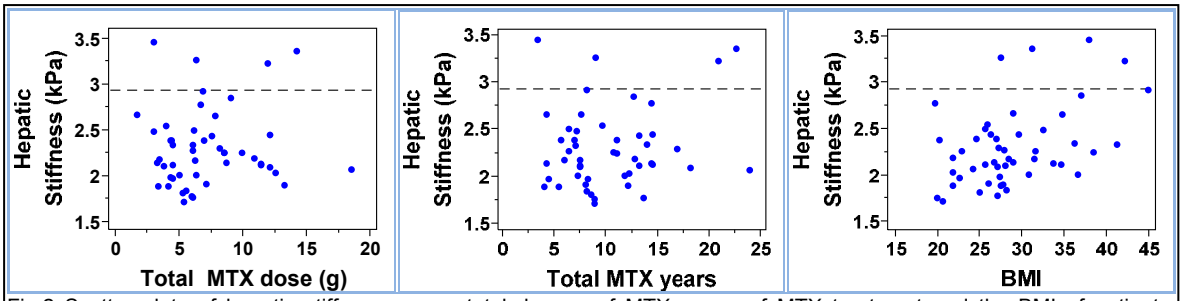

Fig.2 Scatter plots of hepatic stiffness versus total dosage of MTX, years of MTX treatment and the BMI of patients, respectively. The stiffness=2.93 kPa line drawn in the scatter plots was used as a threshold to detect hepatic fibrosis. The hepatic stiffness is the mean value reported by MRE; standard deviation data not shown.

Results and Discussions: MRE was performed successfully on all 49 patients. Fig. 1 shows the magnitude image, wave image and elastogram of one paitient as an example of MRE scan. Fig. 2 shows scatter plots of hepatic stiffness versus total lifetime dose of MTX received by the patients; hepatic stiffness versus total years of MTX treatment and hepatic stiffness versus patient BMI. Overall 5/49 (10.2%) of patients had abnormal hepatic stiffness. Four (8.2%) patients had elevated liver stiffness beyond the 2.93 kPa threshold, the hepatic stiffness of one other patient (2.0%) was just at this threshold. All five patients with abnormal hepatic stiffness patients are obese. Neither total MTX dose received nor number of years of MTX treatment was found to be correlated with elevated hepatic stiffness. Obese (BMI>25) RA patients on MTX treatment may have higher risk of developing liver fibrosis, however this risk can also be due to NASH, which is often correlated with obesity and type 2 diabetes[13]. As part of this study, thus far 4 of 5 patients with abnormal hepatic stiffness have been referred to the Division of Gastroenterology at Mayo Clinic for hepatic disease consultation based on risks other than obesity for developing hepatic disease (i.e. total MTX dose and abnormal laboratory values). Thus far, the 4 selected patients have undergone liver biopsy, one of four patient demonstrating mildly active (grade 1 of 3) steatohepatitis with focal pericellular fibrosis and mild portal fibrosis (stage 1 of 4); 2 of 4 have stage 1-2 fibrosis and 1 of 4 patient has grade 1 inflammation without fibrosis. Further patients will undergo MRE scanning, and a more comprehensive analysis is planned, including the impact of steatohepatitis on MRE findings in obese MTX treated patients with RA. Our findings have potential importance for modifying the current ACR guidelines for frequent liver function monitoring to detect MTX hepatotoxicity among RA patients receiving MTX treatment.

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