Correlation of T1 and T2* Corrected Dual-echo MRI vs. MRS for Hepatic Fat Determination in a Multicenter Clinical Trial: Results of the Phase II Study of the MTP Inhibitor AEGR-733

M. Rosen[1], S. Englander[1], H. Poptani[1], E. Siegelman[1], J. Gimpel[2], D. Flamini[2], M. Parris[3], B. Sasiela[3], and B. Hillman[4]

[1]Radiology, University of Pennsylvania, Philadelphia, PA, United States, [2]American College of Radiology Imaging Network, Philadelphia, PA, United States, [3]Aegerion, Inc., Bridgewater, NJ, United States, [4]Radiology, University of Virginia, Charlottesville, VA, United States

Background: Novel cholesterol lowering medication can be a supplement to statin-based therapies for decreasing serum low-density lipoprotein cholesterol (LDL-C) and triglycerdies (TG). However, these medications may increase hepatic lipid concentration[1,2]. Non-invasive methods for hepatic lipid evaluation include dual- or multi-echo MRI techniques, and single voxel MR spectroscopy (SV-MRS). While SV-MRS is considered the gold standard for hepatic lipid evaluation, MRI evaluation of hepatic lipid may be more feasible, and allows for assessment of heterogeneous lipid accumulation. However, current dual-echo techniques routinely available may not accurately quantify hepatic lipid accumulation[3-4]. In this study, we contrasted the performance of SV-MRS and various dual-echo (DE) MRI methods for quantitation of hepatic lipid in a multi-site trial of a novel lipid lowering agent.

Methods: A phase II trial to study the effects of low doses of the MTP inhibitor AEGR-733 on hepatic lipid accumulation was performed across 15 imaging centers. All potentially eligible patients underwent initial MRI/MRS examination for screening. Those with hepatic lipid levels less than 6.2% by MRS, and who met lipid profile criteria (LDL-C 100-190 mg/dL, TG<400 mg/dL) were randomized to either placebo or one of seven treatment arms using varying dosages of AEGR-733 with or without additional cholesterol modifying agents. Sequential MRI and MRS were then performed pre-therapy and re-evaluated at weeks 4, 8, and 12. There were 470 patients who underwent screening MRI/MRS, and 267 patients enrolled, yielding a total of 1417 combined MRI/MRS data sets.

MRS studies were performed with the body coil using a single voxel PRESS sequence, with a 3cm voxel placed in the right lobe of the liver. Water unsuppressed MRS was performed free breathing using a TR of 3000 ms, TE of 30-35 ms and 16 acquisitions, per previously published protocols[5]. Raw MRS data was processed centrally by a single PhD spectroscopist using NUTS-ACORN software (Acorn NMR Inc., Livermore, CA). FIDs were Fourier transformed without line broadening, and were visually phased and baseline corrected. Water (5.5-3.0 ppm) and lipid (3.0-0.5 ppm) areas were integrated separately to compute the fat-to-total-area (FTSA), and then corrected to determine estimated hepatic lipid fraction by weight[6]. MRS data were deemed unanalyzable if phase or baseline errors prevented accurate integration of peak areas. Analyzable on-study spectra were graded on a 1-5 scale for overall quality.

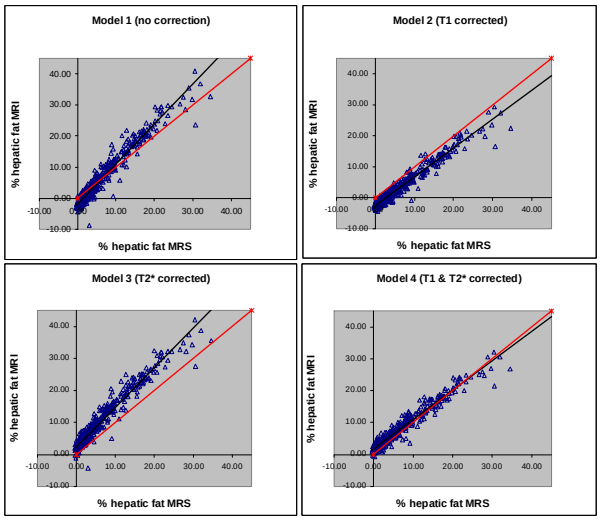
MRI evaluation included three separate breath-held dual-echo 2D spoiled gradient echo series, performed axially through the central portion of the liver. The three sequences included a) opposed-phase(OP)/in-phase(IP) dual echo pair with high flip (T1W), b) OP/IP with low flip (PDW), and IP/2xIP dual-echo pair for T2* mapping (T2*). Compliant MRI data sets were defined as those that met the parameter ranges listed in **Table 1**. The three dual-echo MRI series were evaluated by a single body MR radiologist, who placed an ROI in the right lobe of the liver corresponding to the MRS voxel placement. Hepatic T2* relaxation was estimated by a logarithmic fit to the IP/2xIP signal intensities. FTSA was then estimated through one of four methods based on ROI signal intensity of the T1W or PDW opposed-phase/in-phase image sets (models 1 and 2, respectively), and based on T2* decay corrected ROI signal intensity of the T1W or PDW data sets (models 3 and 4, respectively). MRI-derived FTSA values were converted to estimated lipid fractions as above. For all models, hepatic lipid estimates were correlated with those from MRS. Mean squared deviations from unity and number of outlying data points (MRI and MRS % fat differing by more that 5%) were identified in each data set.

Table 1 Acceptable parameter ranges for MRI dual-echo series

Sequence	TR (ms)	TE1 (ms)	TE2/TE1*	Flip (deg.)
T1W OP/IP	140-260	1.9-2.6	1.8-2.2	70-90
PDW OP/IP	140-260	1.9-2.6	1.8-2.2	10-30
T2* (IP/2xIP)	140-260	3.8-5.2	1.9-2.1	10-90

*acceptable ratio of echo times

Figure 1: Scatter plots of MRI vs. MRS hepatic fat for sets with quality MRS and protocol-compliant MRI. Unity line is shown for comparison.



Results: A total of 470 subjects underwent MRI/MRS screening, and 267 subjects were enrolled across 15 centers. In all, 207 subjects completed the MRI/MRS protocol through week 12, for a total of 1417 MRI/MRS scans. Complete MRI-MRS data sets were available for 1160 exams, of which 1041 exams included MRI-protocol compliant data sets. 596 on-study MRI-compliant data sets had high MRS quality. Mean hepatic lipid content by integrated MRS was 4.5% (range -0.31 % to 34.5%). MRI vs. MRS plots of hepatic fat fraction by model are shown **Figure 1**.

Regression results are shown in **Table 2**. All four methods produced excellent agreement between MRI and MRS. Correlations were stronger for MRI-compliant cases than for all cases, and were stronger still when only exams with higher quality MRS data were used. Among data sets with both quality MRS and compliant MRI, coefficients of determination ranged from 0.949 (model 1) to 0.955 (model 4). Mean squared deviation from unity was lower with model 4 than with models 1-3.

Table 2: Linear regression of MRI vs. MRS

Data source	Model	r^2	Slope	Inter.	MSD[b]	# Out(%)[c]
All MRI/MRS paired data (N=1160)	1	0.890	1.24	-1.98	9.08	67(5.8)
	2	0.870	0.90	-2.70	14.23	103(8.9)
	3	0.906	1.19	+2.41	16.85	224(19.3)
	4	0.880	0.88	+1.71	**5.03**	**22(1.9)**
Compliant MRI data (N=1041)	1	0.935	1.29	-1.97	7.15	51(4.9)
	2	0.938	0.92	-2.63	11.04	63(6.1)
	3	0.939	1.23	+2.37	16.75	210(20.2)
	4	0.942	0.92	+1.73	**3.81**	**10(1.0)**
Compliant MRI with MRS quality 1-3 (N=596)[a]	1	0.949	1.29	-1.75	6.85	27(4.5)
	2	0.953	0.93	-2.49	9.84	26(4.4)
	3	0.950	1.24	+2.50	18.88	142(23.8)
	4	0.955	0.92	+1.79	**3.74**	**6(1.0)**

[a]on-study data sets only [b]mean squared deviation [c]outliers (|MRI-MRS| > 5%)

Conclusion: Multiple dual-echo MRI protocols that allow for both T1 and T2* correction can be used as a surrogate for MRS for quantification of hepatic steatosis in the multisite clinical trial setting. When compared to data from sequences that do not correct for T1 or T2* effects, compensation for both T1 and T2* effects leads to an improved linear correlation between MRI and MRS, the least mean squared deviation from unity, and the fewest number of outlier data points.

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