Liver MRI and MRS for Hepatic Fat Determination in a Multicenter Clinical Trial: Evaluation of Exam Quality in Academic and Non-academic Centers

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[4,5]

[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, [5]American College of Radiology, Phialdelphia, PA, 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 are therefore extremely important for patients undergoing treatment with such agents. While single voxel MR spectroscopy (SV-MRS) is considered a gold standard for hepatic lipid evaluation, MRI evaluation of hepatic lipid may be more feasible in the multi-center setting, and allows for assessment of heterogeneous hepatic lipid accumulation. However, current chemical shift sensitive dual-echo MR imaging techniques routinely available may not accurately quantify hepatic lipid accumulation[3,4]. We compared the performance of SV-MRS and multiple dual-echo MRI in a multi-site trial assessing hepatic lipid quantification, focusing on quality measures of site performance of each study.

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 fifteen participating imaging centers (six academic, nine non-academic). MRI evaluation included three separate breath-held dual-echo 2D spoiled gradient echo series, performed axially through the central portion of the liver: a) opposed-phase(OP)/in-phase(IP) dual echo pair with high flip angle (T1-weighted), b) OP/IP with low flip angle (PD-weighted), and IP/2xIP dual echo pair for estimation of hepatic T2* relaxation. SV-MRS studies were performed using a PRESS sequence, with a 3cm^3 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]. MRI centers without prior experience with MRS were remotely trained by providing them with a "step-by-step" manual for MRS procedures, and all sites were required to submit a single acceptable test SV-MRS study of the liver for qualification. At all sites, shimming for MRS was performed automatically. MRI/MRS examinations at academic sites were not routinely monitored by an in-house physicist. Sites were provided instructions for the MRI protocol, but were not required to submit MRI imaging prior to enrollment. However, MRI protocol adherence was monitored throughout the study, with on-going feed-back given to sites for MRI protocol deviations.

All potentially eligible patients underwent initial MRI/MRS examination for screening. Enrolling patients were then randomized to either placebo or one of seven treatment arms using varying dosages of AEGR-733 with or without additional cholesterol modifying agents. On-study MRI and MRS were then performed pre-therapy and at weeks 4, 8, and 12. On-study MRS raw data was processed centrally using NUTS-ACORN software (Acorn NMR Inc., Livermore, CA) by a single PhD-trained MR spectroscopist, who determined whether spectra were analyzable (i.e. both water and lipid resonances could be separately integrated without excessive phase or baseline errors) and ranked spectral quality on a 1-5 scale based on line-shape and baseline stability (**Figure 1**). MRI quality was assessed centrally through automated checking of the DICOM headers for adherence to MRI protocol (acceptable MRI parameter ranges are shown in **Table 1),** Variation of MRS quality and MRI compliance rates by type of site (academic vs. non-academic) were assessed by chi-squared statistic, and Students t-test, respectively.

Table 1 Acceptable parameter ranges for MRI dual-echo series and SV-MRS

Sequence	TR (ms)	TE1 (ms)	TE2/TE1*	Flip (deg.)	Compliance**
T1W OP/IP	140-260	1.9-2.6	1.8-2.2	70-90	94.9%
PDW OP/IP	140-260	1.9-2.6	1.8-2.2	10-30	95.5%
T2* (IP/2xIP)	140-260	3.8-5.2	1.9-2.1	10-90	95.1%
SV-MRS	3000	30-35	N/A	N/A	96.3%

*acceptable ratio of echo times **for SV-MRS, represents % of analyzable data sets

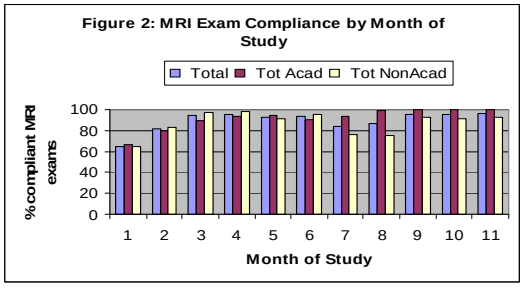
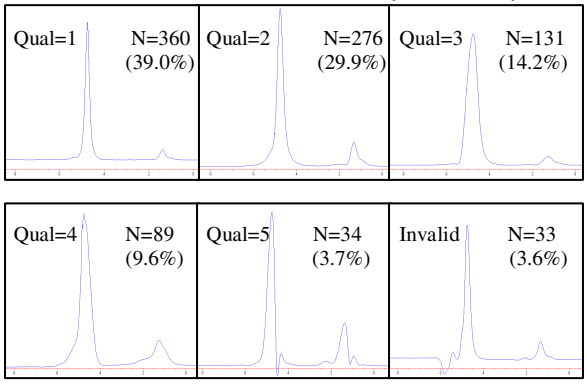


Figure 1: Examples of the varying qualities of submitted SV-MRS. Numerical results are from a total of 923 analyzed "on-study" exams.



Results: A total of 470subjects underwent MRI/MRS screening, for a total of 483 screening MRI/MRS exams (13 repeat eligibility studies were performed due to non-analyzable MRS data). A total of 267 patients were enrolled with 207 patients completing the entire MRI/MRS protocol through week 12, for a total of 934 on-study MRI/MRS exams. Of the 1417 MRS studied performed, one data set was lost electronically by the site and 52 data sets were non-analyzable (total MRS failure rate, 3.7%). A total of five sites had success rates of MRS of 100%. Of the remaining 10 sites, MRS failure rates ranged from 0.8% to 10.5%. The overall MRS failure rate at academic sites was 23/601 (3.8 %) and non-academic sites 30/816 (3.7%, p=NS). MRS quality assessment data was available for 912 on-study MRS exams. Quality scores are shown in **Figure 1**. There was no statistically significant difference between MRS quality scores between academic and non-academic sites (p=0.20)

Of the 1417 MRI scans, rates of acceptable imaging parameters for T1W, PDW, and T2M series were 94.8%, 95.3%, and 95.1%, respectively. Overall, 1276/1417 (90.0%) of the MRI examinations included all three series (T1W, PDW, T2M) with acceptable image parameters. Only five sites submitted fully compliant MRI exams throughout study participation. However, protocol compliance increased as the study progressed (**Figure 2**). The rate of MRI non-compliance was significantly lower (p=0.0002) at academic sites (6.3%) than at non-academic sites (12.6%).

Conclusion: Single-voxel hepatic MRS for hepatic fat quantification can be performed in a multi-site study including non-academic sites with acceptable rates of success. Multi-series dual-echo MRI techniques tailored for quantitative lipid evaluation are also feasible. However, overall MRI protocol compliance was only 90%. Academic sites provided higher levels of MRI protocol compliance than non-academic sites. Active central monitoring of image submission is required to ensure adequate MRI protocol compliance.

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