

Title: SACRED: Effect of simvastatin on hepatic decompensation and death in subjects with high-risk compensated cirrhosis: Statins and Cirrhosis: Reducing Events of Decompensation

Short title: Simvastatin Cirrhosis and Decompensation

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Supplemental Material

Adjudication of Clinical Endpoints

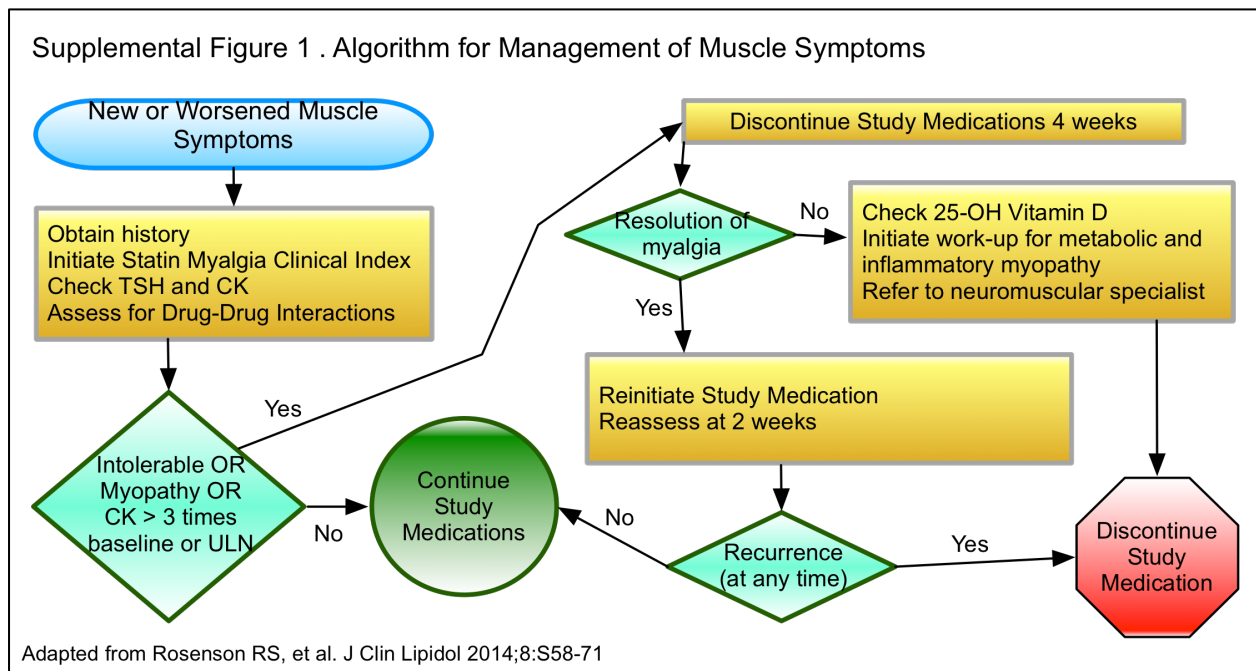
Clinical definitions of the primary outcome are provided. Each outcome will be reviewed by two site clinical investigators from other study sites to validate the outcome event. In the event of disagreement, a third clinical site investigator will be requested to “break the tie.”

- 1) Death will be ascertained by the site research team either through a) direct observation, b) communication from a family member of the decedent, c) communication from hospice providers, d) communication from funeral home, e) notes from other facility providers documenting death, or f) obituary
- 2) Variceal hemorrhage will be defined by documentation of on- or off-site presentation with hematemesis or melena for which upper gastrointestinal endoscopic examination reveals a) active bleeding from an esophageal or gastric varix; b) “white nipple” sign on esophageal or gastric varix; c) evidence of recent hemorrhage with medium-large esophageal varices or gastric varices with high-risk stigmata (cherry red spot, red wale mark, red color signs) with no evidence of alternative bleeding source (such as gastritis, portal gastropathy, gastric ulcer, Mallory-Weiss tear, reflux esophagitis, hemobilia, duodenal ulcer).
- 3) Development of ascites will be defined as a) documentation of a diagnostic or therapeutic paracentesis; or b) clinical examination documenting shifting dullness, bulging flanks and/or fluid wave.
- 4) Development of hepatic encephalopathy will be defined as a) documentation of symptoms consistent with encephalopathy (sleep/wake reversal, fatigue, memory loss, agitation) and presence of asterixis on exam; b) hospitalization with altered mental status deemed to be due to hepatic encephalopathy; or c) initiation of treatment for hepatic encephalopathy with lactulose and rifaximin after documentation of asterixis. Because the diagnosis of hepatic encephalopathy can be subtle and subjective, the site principal investigator will need to adjudicate all cases for which hepatic encephalopathy has been diagnosed by other clinicians.
- 5) The diagnosis of hepatocellular carcinoma will be confirmed by: a) the presence of a 2018 Li-RADs 5 (www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS/CT-MRI-LI-RADS-v2018) radiological observation confirmed by the site principal investigator and/or multidisciplinary liver tumor board; or b) pathological confirmation. If identified by surveillance sonography and confirmed with contrast-enhanced MRI or CT, the date of the sonography will be used as the date of diagnosis.
- 6) Liver transplantation status will be ascertained by the site research team either through a) direct observation, b) communication from a family member of the recipient, or c) communication from the transplant center.
- 7) The occurrence of major adverse cardiac events (acute myocardial infarction, unstable angina, acute ischemic stroke, or coronary revascularization) will be obtained from a) medical record review; b) communication from the patient or family member; or c) communication from clinicians involved in the patient’s care.

- 8) Change in patient health-related quality from baseline to month 12 as assessed by the NIH Patient Reported Outcome questionnaire (PROMIS-29) will be calculated using matched-pair t-test across groups.
- 9) Occurrence of statin-related hepatotoxicity will be defined as documentation of grade ≥ 3 liver toxicity per CTCAE 5.0 (≥ 5 times upper limit of normal as defined by local laboratory).
- 10) Occurrence of myositis/myopathy will be defined as either grade ≥ 3 myositis (pain associated with severe weakness; limiting self-care ADL) OR grade ≥ 4 creatinine phosphokinase by CTCAE 5.0 ($\geq 10x$ upper limit of normal).
- 11) Occurrence of rhabdomyolysis will be defined as grade ≥ 3 (symptomatic, urgent intervention indicated).

Management of Myalgia and Myopathy

Myalgia or Myopathy: Patients who develop muscle-related symptoms during the lead-in phase will not be randomized. For those who develop muscle pain or weakness after randomization, a standardized approach (**Supplemental Figure 1**) will be adopted for evaluation.



Initial evaluation. Standard pain questionnaires perform poorly at differentiating statin-associated versus unassociated muscle symptoms.⁶¹ Statin-related myalgias more commonly involve the lower extremities, occur within 4 weeks of drug exposure, improve upon withdrawal and recur upon rechallenge. We will utilize the Statin Myalgia Clinical Index (SMCI, **Supplemental Table 1**) to assess the likelihood that Myalgia symptoms are statin-related. Patients will undergo physical exam to assess for Myopathy.

Myopathy refers specifically to muscle weakness. We will assess for proximal muscle weakness of the upper and lower extremity using standard clinical grading criteria (5 = normal, 4 = movement against gravity and resistance, 3 = movement against gravity only, 2 = movement when gravity eliminated, 1 = flicker or trace of contraction, 0 = no contraction) at each scheduled visit and upon development of symptoms. Laboratory assessment will include TSH and CK to

evaluate for hypothyroidism and evidence of myonecrosis. Patients with intolerable symptoms OR physical findings of myopathy OR CK greater than 3 times baseline (or 3 times upper limit of normal if no baseline available) will undergo de-challenge for 4 weeks in which no study drug will be taken.

Reassessment: After 4 weeks, if no improvement has been observed, patients will undergo further medical evaluation and study medication discontinued permanently. If symptoms have improved, study medication will be re-initiated and symptom recurrence assessed at 4 weeks. After 4 weeks SMCI will be calculated. All individuals with SMCI ≥ 9 will be defined as having “probable medication-induced myalgia,” and will cease study medication permanently. Individuals with SMCI 7-8 will continue to be monitored for evolution to SMCI ≥ 9 . Subjects with SMCI < 7 will be continued on study medication without further monitoring

Supplemental Table 1. Statin myalgia clinical index score (SMCI)⁶¹

Clinical symptoms (new or increased unexplained muscle symptoms)	POINTS
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Non-specific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks	3
Symptoms onset 4-12 weeks	2
Symptoms onset >12 weeks	1
Dechallenge	
Improves upon withdrawal (<2 weeks)	2
Improves upon withdrawal (2-4 weeks)	1
Does not improve upon withdrawal	0
Rechallenge	
Same symptoms reoccur upon rechallenge <4 weeks	3
Same symptoms reoccur upon rechallenge 4-12 weeks	1
Statin myalgia clinical index score	
Probable	9-11
Possible	7-8
Unlikely	<7

Myositis: Myositis refers to pathological muscle inflammation. Muscle biopsies may be obtained for the evaluation of non-resolving myalgia or myopathy (**Supplemental Figure 1**). If a muscle biopsy is obtained and identifies myositis, this safety endpoint will be considered to have been met.

Myonecrosis: Myonecrosis refers to muscle injury as evidenced by laboratory parameters (CK, aldolase). All abnormalities on CK testing will be confirmed with repeat testing within 24-48h.

Grading: Myonecrosis will be graded as mild, moderate or severe for this study based on lower thresholds for moderate injury than typically applied due to the potential for sarcopenia in the study population.

Mild: CK > 3- and < 5-fold greater than baseline or normative ULN

Moderate: CK \geq 5- and $<$ 50-fold greater than baseline or normative ULN

Severe: CK \geq 50-fold greater than baseline or normative ULN

Assessment: If a patient upon development of symptoms (myalgia or myopathy) or at routine study visits exhibits CK $>$ 5-fold greater than the subject's baseline value in the absence of known triggers (e.g., strenuous activity) which is confirmed on repeat testing, the patient's study medication will be permanently discontinued.

Myonecrosis with myoglobinuria or acute renal failure (increase in serum creatinine \geq 0.5 mg/dl [clinical rhabdomyolysis]) will result in permanent discontinuation of study medication.

Statin-related hepatotoxicity/Drug-induced liver injury (DILI)

Assessment of Baseline: Baseline values of ALT, AST, Total Bilirubin (TBili), Alkaline Phosphatase (ALP), and INR will be obtained from historical values within 6 months of enrollment and at the Screening Visit (at least 2 weeks apart).

If the difference in the two determinations of any laboratory value is greater than 2-fold the upper limit of normal and 2-fold different from the other value, the screening laboratory tests must be repeated prior to randomization to ensure a stable baseline and absence of evidence of acutely worsening liver function. If there is suspicion that a baseline value is an error, then these may be repeated to evaluate for trial entry.

In the event of routine or symptom-related identification of abnormal liver enzymes, the algorithm delineated in **Supplemental Table 2** will be utilized to assess and monitor these findings:

Supplemental Table 2. Assessment and Management of Treatment Emergent Liver Test Abnormalities

Treatment-Emergent ALT	Treatment-Emergent TBili	Liver Symptoms	Action
Normal baseline: ALT $>$ 5x ULN Elevated baseline: ALT $>$ 3x baseline or $>$ 300 U/L (whichever occurs first)	Normal For subjects with Gilbert's syndrome: No change in baseline TBili	None	Repeat ALT, AST, ALP, TBili, in 2–5 days Follow-up for symptoms.
Normal baseline: ALT $>$ 8x ULN Elevated baseline: ALT $>$ 8x baseline or $>$ 500 U/L (whichever occurs first)	Normal Subjects with Gilbert's syndrome: No change in baseline TBili	None	Interrupt study drug. Initiate close monitoring (see the definition below) and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline

Normal baseline: ALT > 5x ULN Elevated baseline: ALT > 3x baseline or > 300 U/L (whichever occurs first)	TBili > 2x ULN For subjects with Gilbert's syndrome: Doubling of direct bilirubin	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Normal baseline: ALT > 5x ULN Elevated baseline: ALT > 3x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBili, total bilirubin; ULN, upper limit of normal. Adapted from Chalasani N, et al. ⁶²			

Close observation/monitoring will be defined as:

- The study medication will be held
- A detailed history for symptoms will be obtained:
 - Appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) will prompt immediate permanent study medication discontinuation.
 - Alcohol consumption will be quantified to assess for concomitant alcoholic hepatitis
 - Concomitant medications, acetaminophen, dietary supplements, herbal remedies, other over the counter medications, recreational drug use, and special diets will be ascertained
 - A history of exposure to environmental chemical agents will be obtained
- Initial treatment:
 - If INR is also elevated, a trial of intravenous vitamin K administration may be considered, especially in cholestatic subjects
- Monitoring:
 - Repeat liver biochemistries and additional testing will be obtained within 24-72 hrs
 - The subject will be monitored every 2-3 days until liver biochemistries (ALT, AST, alkaline phosphatase, total bilirubin, and coagulation profile [INR]) resolve, stabilize or return to within baseline values
 - The subject will then be monitored with liver biochemistry testing once weekly if abnormalities stabilize and the subject is asymptomatic
- Investigational agent must be discontinued, and subject must be followed until the clinical and laboratory abnormalities stabilize or normalize if the following criteria are met:
 - If close monitoring of a subject is not possible.
 - In presence of total bilirubin elevation (>2 x ULN or >1.5 x baseline); with

any degree of aminotransferase elevation; AND if there is appearance of symptoms i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- If any degree of total bilirubin, ALT, or AST elevation recurs following re-challenge with study drug
- Treatment with investigational agent can be re-initiated if treatment emergent abnormalities stabilize, return to pre-trial baseline or normalize.

Adjudication: If treatment-related changes in liver abnormalities (TBili, INR) result in a patient's meeting criteria for Child-Turcotte-Pugh $C \geq 10$ cirrhosis the patient will be considered to have met the Primary Endpoint and study medication will be discontinued.