Is Treatment of Vitamin D Deficiency Associated with Resolution of Statin-Induced Muscular Symptoms

Sponsors: Cedars-Sinai Medical Center CTSI, National Lipid Foundation

Study Investigators: Margo Minissian PhDc, NP, Chrisandra Shufelt, MD, Talya Waldman NP, Caroline Alexander, MD, Puja Mehta, MD FACC, Janet Wei, MD, C. Noel Bairey Merz, MD FACC FAHA

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Section 1.0 General Information

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Section 2.0 Background information

Vitamin D can be found in plants, fortified foods, or be synthesized in the epidermis using ultraviolet B rays.[1] Even with the multiple sources of vitamin D available, an estimated 1 billion people world-wide have deficient or insufficient levels of Vitamin D.[2] The prevalence is higher in urban environments where modern culture res1ults in increased indoor activities and sunblock use as well as ethnic populations where darker skin pigmentation requires increased sunlight exposure to produce an equivalent amount of vitamin D as their lighter skin counterparts.[3,4] Vitamin D is most known for its role in calcium homeostasis. As a patient becomes deficient in vitamin D their calcium stores are depleted and they develop osteomalacia. In addition to bone abnormalities, patients with low vitamin D levels may also develop an osteomalacic myopathy. Low vitamin D stores in these patients are associated with increased body sway, decreased muscular strength, changes in gait, difficulties in rising from a chair, inability to ascend stairs and diffuse muscle pain.[5,6] Longitudinal studies have shown increased risk of falls with increasing amount of musculoskeletal pain intensity and locations.[7] These symptoms of musculoskeletal pain are similar in nature to the muscle pain, or myopathic events, associated with statin use.[8] In fact, patients with statin-induced myopathic events had lower serum vitamin D levels than statin-treated patients without myopathic events.[8] Treatment with vitamin D in both statin-induced myalgic patients and the elderly has shown to reduce the occurrence of myopathic symptoms and falls, respectively.[8,9] Unfortunately, the study by Ahmed et al was a non-randomized trial with subjective patient reporting as the measurable outcome. In addition, the lack of a control prevents assessment of whether these myalgic symptoms would have resolved independently with time. Both these factors may have led to a falsely elevated improvement in statin-induced myalgia; therefore, further randomized control trials are indicated to assess the validity of these findings.

Early in vitro studies have shown the presence of vitamin D receptors (VDR) on muscle cells.[10] In fact VDRs on muscle cells have been shown to decrease with age;[11] similarly, increasing age is a risk factor for developing statin-induced myalgias.[12] Physiologically, vitamin D may directly bind to nuclear receptors in muscle tissue to improve muscle strength or directly increase intracellular phosphate concentrations resulting in increased ATP production and hence improved muscle functioning.[11,13] An alternate theory involves competition of the cytochrome P-450 3A4 (CYP3A4) isozyme that is both responsible for statin metabolism and vitamin D activation. It is theorized that in vitamin D deficient states, CYP3A4 preferentially hydroxylates 25 OH D instead of metabolizing statins, leading to statin-induced toxicity.[14] Statins that most commonly cause myopathic pain (simvastatin and atorvastatin) inhibit the CYP 3A4 system.

Section 3.0 Trial Purpose and Hypothesis

Purpose:

Statins are a highly effective therapeutic intervention for lipid optimization. Compliance is often limited by myopathic pain symptoms. The purpose of this study is to test if treatment with vitamin D can alleviate statin-induced myopathic pain in subjects with serum vitamin D levels ≤ 30ng/mL. This could provide patients a low cost, low risk intervention that would enhance statin compliance.

Hypothesis:

We hypothesize that vitamin D therapy will improve statin-induced myopathic symptoms compared to placebo.

Section 4.0 Trial Design

4.1 Participant Selection and Overall Trial Design

Los Angeles based community physicians and the principal investigator's patients will be recruited for the study. This will serve to attract a primarily urban and ethnically diverse population of subjects. Only outpatients will be used for the study. We will enroll patients with an indication for statin therapy that are experiencing benign, mild to moderate myopathic symptoms such as: myalgia, myositis and myopathy but not rhabdomyolysis but are still able to continue their current statin medication. Rhabdomyolysis will be ruled out with a serum creatine kinase (CK) level < 10 x the upper limit of normal (ULN). These definitions are based on the ACC/AHA/NHLBI guidelines as they are more clearly defined than FDA or NLA definitions for myopathic symptoms related to statin use (Appendix A). Clinician interview will determine that source of pain is myopathic and that myopathic pain is related to statin use. Other etiologies of myopathic pain will be ruled out such as; increased physical activity, hypothyroidism, trauma, falls, accidents, seizure, shaking chills, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).[15] If serum vitamin 25 OH D levels are less than 30ng/mL, then the patient will be eligible for the study, as these patients are considered vitamin D deficient. The patient will continue their current statin regimen and will be randomized to either the placebo arm or treatment arm, which is the Vitamin D arm (Appendix B). All statin medications will be studied in this trial.

4.2 The primary aims of our study include:

1. Assess if treatment of vitamin D deficiency improves statin-induced myopathic pain
2. Assess if treatment of vitamin D deficiency improves statin tolerance3. Assess if treatment of vitamin D deficiency improves the quality of life in patients with statin-induced myopathic pain

4.3 The primary outcomes of our study include:

1. Myopathic pain
2. Quality of life
3. Vitamin 25 OH D levels
4. Statin tolerability

These will be measured used the brief pain inventory (Appendix C), the SF 12 survey (Appendix D), serum measurements, and pill counting, respectively.

4.4 The secondary outcomes of our study include:
1. Parathyroid hormone (PTH)
2. Calcium
3. Lipid profile

PTH and calcium levels are directly dependent on serum 25 OH D levels. In addition, lipid profiles are affected by statin compliance.

4.5 The modifiable variable in our study is:
Number of medications patient is taking that is metabolized by the CYP3A4 enzyme

One of the proposed mechanisms of action in statin-induced myalgia and vitamin D deficiency involve competition at the CYP3A4 enzyme. Therefore, the total amount of CYP3A4 dependent medications each patient consumes will be tabulated to assess if it confounds outcomes at the end of the study. This will be most relevant for those patients who entered the study with a statin that is metabolized utilizing the CYP3A4 enzyme (lovastatin, simvastatin, atorvastatin, rosuvastatin, fluvastatin). Because 3 of these 5 statins are available in generic formulation, they will most likely be prescribed at a higher frequency in our urban dwelling population. This will be done with a medication list review (Appendix E).

4.6 Study population
Recruitment of patients will occur during outpatient clinic visits and through outpatient referrals from Los Angeles-based community physicians. Community physicians will not be sharing detailed study information with patients. Our study population will consist of 40 male and female urban dwelling patients of varied ethnic origin. Although women are preferentially affected by osteoporosis and the phenomenon under study may be similar to osteomalacic myopathy, we will include men in the study for inclusiveness All women of child bearing age included in the study must be using an effective form of contraception because statin therapy can be harmful to a growing fetus. These women are all already on statin therapy so they cannot be pregnant as per clinical care. However, to ensure patient safety, all women will undergo urine pregnancy testing at the beginning of the study. Lactating women, however, can transmit statins to children through breast milk; therefore, they will be excluded from our study.

4.7 Safety
In order to assess if patients meet all inclusion and exclusion criteria, the patient will have to be interviewed, their chart reviewed, blood pressure measured, and have a urine pregnancy test (child bearing women). To ensure it is safe for the patient to begin the study, the chart will be reviewed to ensure baseline laboratory values within the last 6 months are within normal limits: creatinine (Cr), calcium (Ca), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (alb). Serum thyroid-stimulating hormone (TSH) values need to be within normal limits within the last 12 months. If these labs are not current, they will be re-drawn at the beginning of the study. Blood pressure will be measured prior to initiation of study since some research suggests that vitamin D therapy can lower blood pressure.[16] Finally, the patient will have to be interviewed to assess if they meet all inclusion and exclusion criteria.

4.8 Course of Experiment

During the patients routinely scheduled clinical care visit or at time of referral, the patient will be screened for study eligibility. Patients on any statin will be included. Patient must have clinically documented vitamin D level <30ng/mL within 6 months of study entry during screen. It will be determined during the screen that patients' myalgia symptoms are due to statin therapy and that patient is able to continue their current statin medication. Once all the inclusion/exclusion criteria are met, the patient is recruited into the study and scheduled for their first research visit. At research visit #1, patients will be consented for the study, have lab work drawn for safety and laboratory outcome measurements (primary and secondary outcomes), complete study surveys (SF-12 and BPI), medical history, and medication review documents. They will also undergo a physical exam where blood pressure, height, weight, vital signs, abdominal and hip circumference measurements will be taken. The patient will then be randomized to either a treatment or placebo group and given the study drug. The study will be double-blinded. The treatment group will receive Ergocalciferol therapy at 50,000IU for 8 weeks while the placebo group will receive a placebo pill that is identical in nature. Patients will be asked to continue their current statin. Once serum creatinine, calcium, urine pregnancy (child bearing women) if indicated and creatine kinase levels return, likely within the same day, patient will be given a phone call and asked to start study drug or placebo for the next 8 weeks. Patients will then be called by study investigators and/or coordinator in 1-2 weeks for a phone follow-up where tolerability of study drug will be discussed as well as discussion and documentation of any adverse events (AEs). During this phone call an exit appointment will be scheduled after completion of 8 week course of study drug vs placebo. If patient is unable to tolerate protocol an earlier exit visit will be scheduled. During the exit visit patient will undergo a repeat physical exam, complete surveys and medication review, and phlebotomy that will measure the primary outcomes, secondary outcomes, modifiable variables, and safety measurements: creatinine, calcium, and creatine kinase levels. For a temporal summary, please refer to Appendix G.

Section 5.0. Selection and Withdrawal of Subjects

Patients experiencing myopathic pain while consuming any statin medication will be approached by one of the study investigators regarding their participation. The study will be explained to them and if they would like to participate in the study the patient will be given a consent form to review. The patient will be given the opportunity to ask any questions. After all questions have been answered and the patient appears to fully understand the study, they will be offered additional time to think about participation and go over the study material. The patient will be given the contact information for the study investigator in order to ask additional questions. After all questions are answered, and the patient has fully reviewed the consent and decides to participate, the patient will be scheduled for her first research visit at which time written consent will be obtained.

5.1 Inclusion Criteria:

Only patients meeting all the listed criteria below will be asked to participate

2. Age > 18, using an effective form of contraception (refer to section 4)
3. An indication to be on statin therapy
4. Mild to moderate myopathic pain while on a statin
5. Pt able to continue current statin

6. Serum CK level < 10 x ULN
7. Vitamin 25 OH D level <30 ng/mL (as secondary hyperparathyroidism is triggered below this level)[2]
8. English speaking patients only
9. Myopathic pain that cannot be attributed to other medical conditions
10. Continue a statin within the CYP3A4 family
11. Competent to give informed consent
12. Vitamin D Level <30ng/mL
13. (+)Myalgia symptoms on a statin medication
14. Negative pregnancy test

5.2 Exclusion Criteria:

1. Clinical diagnosis of overt vitamin D deficiency: osteomalacia, rickets, hypocalcemia, hypophosphatemia
2. Already taking Vitamin D supplements >1000 IU/day
3. Serum creatinine> 2.2 mg/dL within last 6 months
4. AST/ALT > 3 x ULN of the local reference range
5. Serum CK level > 10 x ULN
6. Systolic blood pressure <90 mmHg
7. Albumin adjusted calcium >2.55 mmol/L or <2.20 mmol/L
8. Renal osteodystrophy
9. Malabsorption syndrome
10. Metastatic malignancy
11. Transplant recipients
12. A co-existent diagnosis of renal calculi within the previous 6 months
13. A co-existent diagnosis of primary hyperparathyroidism within the previous 6 months
14. Recent therapy with corticosteroids within the previous 6 months
15. Currently consuming Digoxin, as usage increases risk of hypercalcemia
16. Lactating women (refer to section 4)

5.3 Withdrawal Criteria

Patients who are severely intolerant to their current statin therapy, meaning hydration and rest do not improve symptoms, will be asked to exit the protocol. Patients will be brought back for their exit visits outlined in Appendix G and data regarding all measurable outcomes will be taken. In addition, remainder study drug will be collected. Patient will then be referred to primary care physician for further management of vitamin D deficiency, if persistent. In regards to statin management, patients will be withdrawn from their current statin and asked to follow up with their cardiologist or primary care physician for further statin therapy management.

Section 6.0 Treatment of Subjects

Study Drug

The intervention under study in this trial will be ergocalciferol, vitamin D2. Of the 40 patients selected for the study, 20 will be randomized to the treatment group while the other 20 will be randomized to a placebo group. During this time they will also be encouraged to continue taking their current medication regimen and supplemental regimen as long as the cumulative Vitamin D

dose is <1000 IU/day. Vitamin D is currently not a standard medical intervention in the treatment of myopathic pain. Vitamin D, in this study, is being used to treat patients with low serum 25 OH D levels. In addition, assessing for vitamin D deficiency is not routine and there is no consensus on who should be offered therapy; therefore, since the study extends for a short period of time, it is safe for deficient patients to be randomized to the placebo arm. Furthermore, upon completion of the study, patients who were vitamin D deficient and randomized to the placebo arm will be offered therapeutic doses of vitamin D.

Currently, there is no consensus on an optimal serum 25 OH-D level in asymptomatic insufficient patients. Optimal serum goals are set based on overt symptoms of deficiency which typically occur at levels <15 ng/mL. Therefore, the current standard of care is to treat patients with high dose ergocalciferol to keep levels at least >20ng/mL but ideally >30ng/mL as secondary hyperparathyroidism is prevented at these serum concentrations. Since we are testing whether vitamin D supplementation will improve statin-related myalgias in subjects with low serum vitamin D levels, we have planned our study feasibility based on a 30ng/mL threshold. Ergocalciferol is the current standard of care for treating vitamin D deficiency. Since we are using ergocalciferol therapy to treat vitamin D deficiency, and because our trial is a pilot study, the data will not be submitted to the FDA for consideration of changing the labeled indications for ergocalciferol therapy.

Section 8.0 Assessment of Safety

When the vitamin D system is overstimulated, hypercalcemia results because of increased intestinal calcium absorption and by the induction of bone re-absorption. In regards to vitamin D, hypercalcemia is the criterion for harm, because it is the agent that causes symptoms.[17] These symptoms include nausea, dehydration, lethargy, weakness, excessive thirst, anorexia, headache, constipation, weight loss, kidney stones, arterial calcium deposits and decreased or altered urine output. However, toxicity is a rare concern with vitamin D, especially since UVB rays degrade excess vitamin D.[2] Serum 25 OH vitamin D levels are measured approximately 2 months after initiation of high dose ergocalciferol therapy to monitor efficacy as well as toxicity. This time period is consistent with the termination of our study, where we will obtain serum calcium and 25 OH-D levels to monitor efficacy and toxicity. Furthermore, the first signs of toxicity typically do not occur until a serum 25 OH D concentration of 100-140 ng/mL (>250nmol/L),[18] which is unlikely to be obtained at high doses prior to the 3 month monitoring period that is currently the standard of care.[19]

Statins, although rare, can cause rhabdomyolysis. This is the main concern when patients develop myopathic pain. If serum CK levels are > 10 x ULN then the patient is toxic from statin therapy, and further therapy with statins should be discontinued. Prior to study initiation, serum CK levels will be checked to screen out patients with rhabdomyolysis in whom continuation of statins is unsafe.

Section 9.0. Statistics

Our goal sample size of enrolled patients is 40, with 20 patients in each arm. We approximate 10% of patients that we approach regarding the study will actually meet all inclusion and exclusion criteria as well as agree to the study; therefore, we estimate that we will have to approach approximately 400 patients.

9.1 DataAnalysis for Baseline Comparability. To establish comparability between the groups at baseline, all subjects randomized will be compared with respect to the baseline variables, including the primary and secondary outcome variables, demographics, reproductive history, risk factors, medical history, current medications, and physical exam variables. Comparisons between treatment groups will be performed using two sample t-test for normally-distributed continuous variables, Wilcoxan rank-sum test for non-normal or ordinal data, and Chi-square test for categorical variables. To evaluate whether a variable follows a normal distribution, we will use the Q-Q plot and Kolmogorov-Smirnov test.

9.2. Data analysis to assess group difference at exit. If there is no systematic group difference in the primary and secondary outcome variables at baseline, comparisons of these variables between the groups will be conducted using measurements taken at study exit. Two sample t-test will be used for normally-distributed variables, Wilcoxon rank-sum test for non-normal or ordinal data, and Chi-square test for categorical variables. For variables that show group differences at baseline, change scores will be used in the above analysis. Change scores will be calculated as the difference between study exit and baseline. Secondary analysis to assess group difference will be carried out using regression models to adjust for baseline covariates/factors that show group difference in 9.1. The outcomes in the regression analysis are the measurements at exit or change scores. We will use linear regression for continuous outcome variables (may be subject to transformation), logistic regression for binary variables, and proportional odds models for ordinal data.

9.3 Study Power. This is a pilot study, so a formal sample size calculation for statistical power is not included. Estimates of between-group difference and data variability will be used to conduct a more definitive sample size calculation for a larger study.

Section 11.0 Ethical considerations relating to the trial

All participation is voluntary. Patients will have the study explained to them in detail and be allowed to ask questions to allow for informed consent. Patient charts will be reviewed and all information regarding the patient will be kept confidential. **Since the study extends for a short period of time, it is safe for deficient patients to be randomized to the placebo arm. Upon completion of the study, patients who were vitamin D deficient and randomized to the placebo arm will be offered therapeutic doses of vitamin D.** Risk of side effects is extremely low and benefits of therapy are high, favoring the risk benefit ratio towards treatment with vitamin D. There are no potential conflicts of interest.

Section 12.0. Data Handling and Recordkeeping

All personal identifiable information will be kept confidential. All data collected will be handled by the study investigators only and kept confidential. No personal information regarding patients will be stored on personal computers.

Section 13.0. Financing and Insurance

The patient will not incur any additional costs by participating in this study. All interventions initiated by this research protocol will be covered by the study investigators source of funding, which currently remains to be determined.

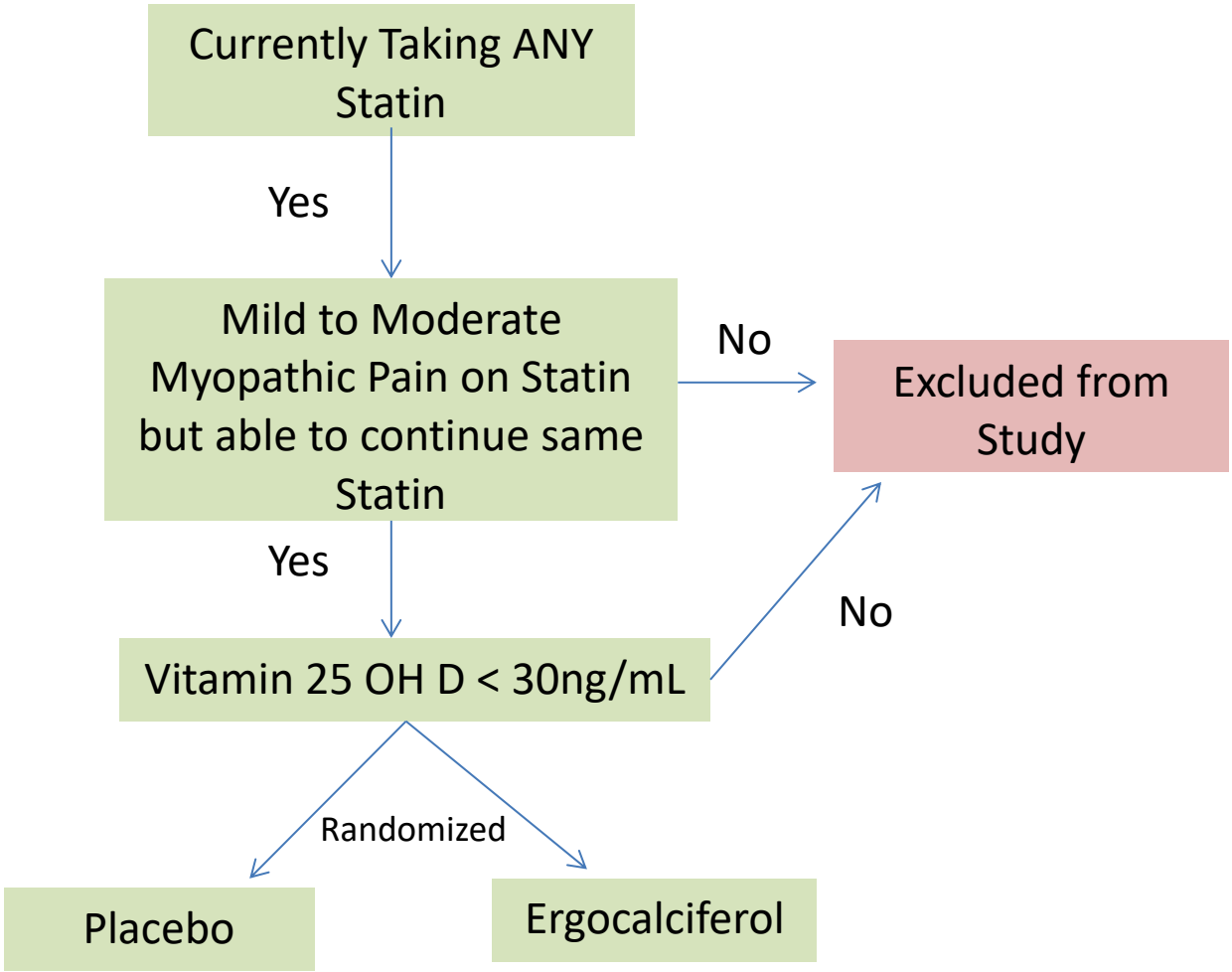
Appendix A

Table 1. **Proposed Definitions for Statin-Related Myopathy**

Clinical Entity	ACC/AHA/NHLBI (2)	NLA (4)	FDA (3)
Myopathy	General term referring to any disease of muscles	Symptoms of myalgia (muscle pain or soreness), weakness, or cramps, plus creatine kinase >10 × ULN	Creatine kinase ≥10 × ULN
Myalgia	Muscle ache or weakness without creatine kinase elevation	NA	NA
Myositis	Muscle symptoms with creatine kinase elevation	NA	NA
Rhabdomyolysis	Muscle symptoms with significant creatine kinase elevation (typically >10 × ULN), and creatinine elevation (usually with brown urine and urinary myoglobin)	Creatine kinase >10 000 IU/L or creatine kinase >10 × ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration	Creatine kinase >50 × ULN and evidence of organ damage, such as renal compromise

ACC/AHA/NHLBI = American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute; FDA = U.S. Food and Drug Administration; NA = not available; NLA = National Lipid Association; ULN = upper limit of normal.

Appendix B- Study Design



Appendix C

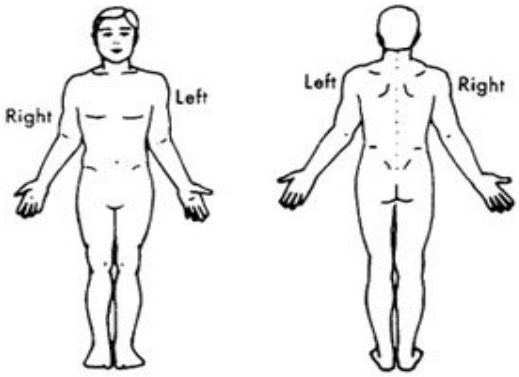
FORM 3.2 **Brief Pain Inventory**

Date____ / ____ / ____ Time:_____

Name: _____ _____ _____
Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
1. Yes 2. No

2) On the diagram shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **worst** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **least** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **average**

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
No pain — pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

_____

8) In the Past 24 hours, how much **relief** have pain treatments or medications provided? Please circle the one percentage that most shows how much releif you have received

0% 10 20 30 40 50 60 70 80 90 100%
No relief — Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has **interfered** with your:
A. General activity

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

Medscape Source: Pain Manag Nurs © 2008 W.B. Saunders

Appendix A. Brief Pain Inventory: measures pain from chronic diseases to assess the severity and impact of pain on daily life. The short form survey has a Cronbach alpha reliability ranging from 0.77 to 0.91. This survey takes approximately 5 minutes to fill out

Reference: ICH E6: Good Clinical Practice: Consolidated Guidance

Appendix D

SF-12® Patient Questionnaire (Page 1 of 3)

This information will help your doctors keep track of how you feel and how well you are able to do your usual activities. Answer every question by placing a check mark on the line in front of the appropriate answer. It is not specific for arthritis. If you are unsure about how to answer a question, please give the best answer you can and make a written comment beside your answer.

1. In general, would you say your health is:

_____ Excellent (1)
_____ Very Good (2)
_____ Good (3)
_____ Fair (4)
_____ Poor (5)

The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

2. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playinggolf:
_____ Yes, Limited ALot (1)
_____ Yes, Limited A Little (2)
_____ No, Not Limited At All (3)

3. Climbing SEVERAL flights of stairs:
_____ Yes, Limited ALot (1)
_____ Yes, Limited A Little (2)
_____ No, Not Limited At All (3)

During the PAST 4 WEEKS have you had any of the following problems with your work or other regular activities AS A RESULT OF YOUR PHYSICAL HEALTH?

4. ACCOMPLISHED LESS than you would like:
_____ Yes (1)
_____ No (2)
5. Were limited in the KIND of work or other activities:
_____ Yes (1)
_____ No (2)

During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

6. ACCOMPLISHED LESS than you would like:
_____ Yes (1)
_____ No (2)

7. Didn't do work or other activities as CAREFULLY as usual:
_____ Yes (1)
_____ No (2)

8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?
_____ Not At All (1)
_____ A Little Bit (2)
_____ Moderately (3)
_____ Quite A Bit (4)
_____ Extremely (5)

The next three questions are about how you feel and how things have been DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS –

9. Have you felt calm and peaceful?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

10. Did you have a lot of energy?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

11. Have you felt downhearted and blue?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

12. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?
_____ All of the Time (1)
_____ Most of the Time (2)
_____ A Good Bit of the Time (3)
_____ Some of the Time (4)
_____ A Little of the Time (5)
_____ None of the Time (6)

Appendix E CYP3A4 Medication List

CYP3A4 Medicine	Study Onset	Study Completion
Amiodarone		
Amlodipine		
Carbamazepine		
Clopidogrel		
Diltiazem		
Fluconazole		
Fluoxetine		
Esomeprazole		
Gemfibrozil		
Nifedipine		
Phenytoin		
Rifampin		
Verapamil		
Mibefradil (posicor)		
Ezetimibe		
Niacin		
Sildenafil		
Quinidine		
Clarithromycin		
Erythromycin		
Ketoconazole		
Itraconoazole		
Terbinafine		
Protease Inhibitors		
Cyclosporine		
Nefazodone		
Midazolam		
Supplement w/Vitamin D and corresponding dose		
Total		

Appendix G: **FLOWCHART OFPROCEDURES**	**Screen Visit**	**Initial Research Visit #1 Week 0**	**Visit #2 Phone Follow-up Week 1-2**	**Visit #3 (Week 8)**
Standard of Care Procedures: Procedures that are part of regular care and would be done even if you did not take part in this research study				
Confirm myopathic pain from statin	X			
Medical record review, labs: ast/alt/alb/ca/cr/tsh, vital signs	X			
Chart review vitamin 25 OH D < 30ng/mL	X			
Research Related Procedures: Procedures, drugs, devices, evaluations or other services done only because of your participation in this research.				
Review Inclusion/Exclusion Criteria	X			
Consent		X		
Physical Exam: including vital signs, height, weight, abdominal and hip circumference		X		X
Safety Measurements Phlebotomy: Creatine kinase (ck) Creatinine (cr)Calcium (Ca) Urine Pregnancy (U-Bhcg)		X X X X		X X X
Primary and Secondary Measurements w/Phlebotomy: intact PTH, Ca, vitamin 25 OH D, total cholesterol, LDL, HDL		X		X
Primary outcomes survey measurements: SF-12, Brief Pain Inventory		X		X
Modifiable Variables Measurements: Medication Review: CYP3A4 medications, Supplement review		X		X
Initiation of Medication: Ergocalciferol vs Placebo		X		

Phone Follow-up: discuss tolerability of medications and evidence of any adverse events			X	

Appendix H Characterization of Vitamin D levels

25-OH D Level	ng/mL (=microg/L) (used in USA)	nmol/L (used internationally)
Deficient	<10	<25
Insufficient	10-20	25-50
Hypovitaminosis	>20-32/40	>50-100
Adequate	>40-100	>100-250
Toxic	>100/140	>250

*These values are used merely for definition. There is limited consensus on the definition of varying serum 25 OH D levels.[20] Internationally, 25 OH D is reported in nmol/L. In the US, it is reported in ng/mL (or microg/L). To convert ng/mL to nmol/L, multiply by the conversion factor 2.496. To convert from nmol/L to ng/mL divide by the conversion factor 2.496.

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