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Strategies to Continue Statin Use in Patients with Myalgia

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Abstract

Nothing has proven to be as effective in the treatment of coronary heart disease as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, and since heart disease continues to be the leading cause of death in the United States, it is imperative for patients to be able to tolerate and maintain statin therapy. Even though statins are known to have an impressive safety profile and are generally well tolerated, discontinuation of therapy does occur, and is most often due to myalgia symptoms. The patient presented in the case report was diagnosed with familial hypercholesterolemia, and statin therapy is a vital piece of the treatment plan. The goal of this literature review is to evaluate both alternative statin dosing and vitamin D supplementation to determine if using either of these strategies allows patients to continue statin therapy, thus reducing both morbidity and mortality by decreasing the risk of future cardiovascular events.

Background and Rationale

Heart disease, accounting for 600,000 deaths annually, continues to be the leading cause of death in the United States. Hypercholesterolemia is one of the major risk factors for developing heart disease (Centers for Disease Control and Prevention, [CDC], 2014). Additionally, according to the CDC (2014), "Several genetic disorders are associated with increased risk of premature heart attacks. A relatively common disorder is familial hypercholesterolemia, which causes high levels of 'bad' cholesterol (low density lipoprotein, or LDL cholesterol) beginning at birth" (para. 2). Cholesterol, a fat-like, waxy substance, is a component of all body cells. It plays a necessary role in the production of hormones and vitamin D, as well as aiding in food digestion. Our bodies are capable of making all the cholesterol it needs to carry out these functions. Therefore, the additional cholesterol found in dietary sources needs to be removed via high-density lipoproteins, or HDL, which is often referred to as the "good" cholesterol. The "bad" cholesterol, or LDL as mentioned previously, causes buildup of plaque leading to atherosclerosis, which results in a decrease of oxygen-rich blood flow through the arteries supplying the heart and thus the rest of the body (National Heart, Lung, and Blood Institute, [NHLBI], 2014). This process leads to coronary artery disease (CAD) also called coronary heart disease (CHD), the most common form of heart disease (CDC, 2015; NHLBI, 2014). Coronary heart disease can lead to heart failure, arrhythmias, heart attack, and stroke (NHLBI, 2015).

Sully, a 24-year-old male and the patient presented in this case report, was diagnosed with familial hypercholesterolemia. This inherited condition of elevated

cholesterol can cause CAD leading to heart attacks at an early age (National Human Genome Research Institute, [NHGRI], 2013). According to the NHGRI (2013), "Men who have familial hypercholesterolemia have heart attacks in their 40's to 50's, and 85 percent of men with the disorder have a heart attack by age 60," (What is familial hypercholesterolemia, para. 5). The inherited condition is a result of a gene mutation on chromosome number 19, which is responsible for removing LDL from the bloodstream. This alteration results in high levels of LDL beginning at birth (NHGRI, 2013). The fasting lipid panel drawn on the patient in this case report revealed elevated cholesterol and LDL; additionally, his father also had hypercholesterolemia and died of a heart attack at the age of 55. These factors led to the familial hypercholesterolemia diagnosis.

The treatment of familial hypercholesterolemia has several aspects including diet, exercise, weight management, and medication (NHLBI, 2005). Statins are generally the medication of choice in hypercholesterolemia treatment (Reinhart & Woods, 2012). Statins inhibit cholesterol formation in the liver along with increasing liver cell receptors that are responsible for removing LDL from the bloodstream (Gotto, 2002). Studies have shown statins to decrease LDL by 20 to 40%, and in some cases by even greater than 40% depending on the drug and dosage (Weng, Kao Yang, Lin, & Tai, 2009). Even though statins are generally well tolerated, studies have revealed that as many as 20% of patients discontinue use due to reported myalgias. This adverse side effect of statin therapy is not well understood, and it can be challenging to differentiate it from other possible causes. Clinically, myalgias are of concern due to the risk of rhabdomyolysis, which is severe

muscle damage that can lead to kidney damage and even death (Reinhart & Woods, 2012; Thompson, Clarkson, & Rosenson, 2006). The efficacy of alternative therapies has not proven to equal that of statins, specifically when speaking "in terms of mortality risk reduction" (Reinhart & Woods, 2012, p. 292). As stated by Reinhart and Woods (2012), "any strategy capable of preventing repeat myalgia in these patients will help enable their continued use of statin medication and help lower the morbidity and mortality associated with CHD" (p. 292). Alternative dosing and adding vitamin D supplementation to reduce myalgia symptoms and maintain statin therapy are two strategies that have been studied. Therefore, the purpose of this literature review is to determine if either strategy will effectively assist in the goal of continuing statin therapy in patients with reported myalgia.

Case Report

Chief Complaint: requesting cholesterol check r/t family history

HPI: This 24-year-old male presents today requesting to have his cholesterol checked. Patient states his mother encouraged him to come in because his father, who had elevated cholesterol, recently died of a heart attack. Patient denies chest pain, palpitations, hypertension, or shortness of breath.

Past Medical History: allergic rhinitis

Past Surgical History: tonsillectomy and adenoidectomy at age 4

Family History: Father – died at age 55 from a heart attack, Mother – alive and well, Brother – hypercholesterolemia, age 27

Social History: Patient is an EMT and does shift work. Reports exercising for 30 minutes 4-5 days per week. Patient denies caffeine intake, smoking, and recreational drug use. Reports frequent fast food intake and drinks 2 beers each evening along with social drinking 1-2 weekends per month where he consumes 5-6 drinks on those occasions.

Medications: Zyrtec prn

Allergies: NKA

ROS:
Constitutional: denies fatigue, recent weight change, fever, trouble sleeping
Cardiovascular: denies chest pain, palpitations, hypertension, edema
Respiratory: denies shortness of breath
Psychological: denies anxiety, depression, mood changes

Physical Exam:
Vitals: BP 110/54, HR 62, Temp 37.1 c, Ht 6'1", Wt 200 lbs., BMI 26.4
General: alert, well developed, no acute distress
Skin: color normal
Cardiovascular: S1 and S2, no murmurs, regular rate, no JVD or edema noted
Respiratory: respiration rhythm and depth normal, clear to auscultation
Psychiatric: normal affect, normal mood

Labs:

Lipid panel:
Cholesterol – 310
Triglycerides – 140
HDL – 60
LDL – 209

BMP:
BUN – 18
Sodium – 139
Potassium – 3.9
Chloride – 102
CO2 – 27.3
Glucose – 86
Creatinine – 1.1
Calcium – 9.8
Anion gap – 9.7
GFR - >60
Albumin – 4.00
Alk Phos – 88
Total Protein – 7.4

LFT:
Albumin – 4.0
Alk Phos - 88
Total bili – 0.4
AST - 20
ALT - 22
Total protein – 7.4

Impression/Plan:
1. Familial Hypercholesterolemia – start Lipitor 20mg daily, discussed importance of compliance and medication side effects, follow a low cholesterol diet and reduce saturated fat intake, continue exercise regimen, maintain weight.

Patient verbalized understanding of above plan and is agreeable. Patient encouraged to call with any questions or concerns.

Follow-up in 3 months with fasting labs. Will recheck lipid panel. Will consider dietary consult at this time.

Literature Search Strategy

A literature search was conducted utilizing both CINAHL and PubMed databases via the University of North Dakota Harley E. French Library of the Health Sciences website. An advanced search in PubMed was completed using the medical subject heading (MeSH) terms of "statins" AND "alternate dosing." The search generated 22 articles. The "English language" and "published within the last 10 years" filters were added, reducing the articles to 17. After reviewing all 17 articles, one appeared to be most related to the clinical question but was not included in this review; however, the "similar articles" feature attached to this particular article was utilized and an additional 136 articles were generated. After reviewing the articles, three were determined to be relevant. Review of the reference sections of the three articles resulted in two additional articles, which were retrieved using PubMed. An additional search in PubMed using the MeSH terms of "statin intolerance" AND "vitamin D supplementation" and again including the "English language" and "published within the last 10 years" filters, generated eight articles for review. Two of these articles were determined to be pertinent to the research question. An additional article was found and retrieved via PubMed after review of the reference sections. The CINAHL search was conducted using the search terms "statin" AND "myalgia." This search resulted in 67 articles. The "English language" and "published within the last 10 years" filters were added reducing the articles to 57. After review, one was found to be pertinent to the research question, and one additional article was obtained via PubMed after review of the reference section. Thus, the literature search produced a total of 10 articles.

Literature Review

Alternative Dosing

Patient benefit from statin therapy is well documented, and research has proven that it is essential in the treatment of CHD especially in reducing morbidity and mortality. Statin intolerance due to myalgia often leads to discontinuation of this life-saving medication. Alternative statin dosing is one strategy that has been studied to determine if it leads to decreased intolerance, thus allowing patients to continue on therapy (Reinhart & Woods, 2012). Rosuvastatin and atorvastatin are the two medications most often studied as their long half-life provides the greatest chance to achieve therapeutic levels with less frequent dosing (Gadarla, Kearns, & Thompson, 2008; Kennedy, Barnas, Schmidt, Glisczinski, & Paniagua, 2011). In the randomized controlled trial (RCT) presented by Kennedy et al. (2011), 17 patients were evaluated. The patients all had a diagnosis of hypercholesterolemia and were deemed statin intolerant due to myalgia. The patients were not currently on statin therapy and were not meeting LDL goals according to the Adult Treatment Panel III (ATP III) National Cholesterol Education Panel (NCEP) Guidelines. The study had two eight-week phases and the participants switched treatment arms after the first phase. Patients were given once-weekly rosuvastatin 5 mg or a placebo for four weeks, and if they were not at LDL goal after the first four weeks, the dose was increased to 10 mg. Patients were required to remain consistent with their lifestyle habits throughout the study. A 12.2% reduction in LDL was noted in the patients who were given once-weekly rosuvastatin versus 0.4% reduction in the placebo group, and 20% attained LDL goal while zero patients met goal on placebo.

Furthermore, 11.8% of patients reported myalgia while on the placebo treatment, and 20% reported myalgia while on rosuvastatin leading to therapy cessation (Kennedy et al., 2011). The authors concluded, "Once-weekly low-dose rosuvastatin is an effective and well-tolerated lipid-lowering therapy option for patients not at LDL goal and previously unable to tolerate statins because of a history of myalgias" (Kennedy et al., 2011, p. 308).

In an RCT conducted by Jafari, Ebrahimi, Ahmadi-Kashani, Balian, and Bashir (2003), 54 patients were included in the study after meeting the criteria of an LDL ranging from 100 to 200 mg/dL as well as meeting the parameters considered appropriate for treatment per the NCEP guidelines. Therefore, patients with abnormal liver enzymes or creatine kinase (CK), patients currently taking another cholesterol-reducing medication, those pregnant or breastfeeding, or those who experienced previous intolerance to statin therapy were excluded. The six-week trial included three randomized groups who received either atorvastatin 10 mg every day, 10 mg every other day, or 20 mg every other day. The groups were relatively similar when considering age, gender, and weight. Out of 54 patients, 46 finished the study. Those who did not complete the study did not come to their six-week follow-up and were thus labeled as dropouts. Patients were evaluated with fasting lipids, liver function, and CK tests. All three groups saw a significant reduction in LDL and total cholesterol, and those who took atorvastatin 20 mg every other day also experienced a significant increase in HDL. All regimens evaluated were deemed well tolerated as no myalgia was reported, no significant increase in liver enzymes or CK was noted, and therapy compliance was achieved. These study

results indicate that alternate atorvastatin dosing is effective and safe (Jafari et al., 2003).

A RCT evaluating 35 patients was conducted by Matalka, Ravnan, and Deedwania (2002). The study required diagnosed hypercholesterolemia participants to be at least 18 years of age and to meet NCEP ATP II treatment guidelines. If patients were currently taking a cholesterol-lowering medication, the medication was discontinued and the study was started six weeks later. Patients were excluded with triglycerides over 400 mg/dL, uncontrolled diabetes with blood glucose greater than 200 mg/dL, or three-month history of either myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. The study also excluded patients with liver enzymes greater than three times the upper limit of normal, those who consume more than 10 alcoholic beverages per week, along with those taking azole antifungal medications, warfarin, or any immunosuppressants. The patients were assigned randomly to receive either atorvastatin 10 mg every day or every other day for a period of 12 weeks. The dose was doubled at the six-week interval if the patient was not meeting LDL goal. Lipid levels were assessed at baseline, six weeks, and again at 12 weeks. Additional labs were drawn in order to evaluate safety, which included a complete blood count, chemistry panel, CK, and liver function tests. At the six-week point, patients showed an LDL reduction of 27% in the alternate-day group and 38% in the every-day group. Results at the 12-week interval included a 35% LDL reduction in the alternate-day group and a 38% reduction in the every-day group. Unfortunately, there was also a decrease in HDL at 12 weeks in both groups. The dose was doubled

in 79% of those taking atorvastatin every other day compared to 17% of the patients taking the medication daily. Goal in LDL levels was achieved by 43% of those in the alternate-day group versus 75% of patients in the every-day group. Only one patient had to be withdrawn from the study due to muscle weakness (Matalka, Ravnan, & Deedwania, 2002). As stated by Matalka, Ravnan, and Deedwania (2002), "The study showed that the efficacy of alternate-day administration of atorvastatin is comparable to that of daily administration in reducing LDL-C in patients with hypercholesterolemia" (p. 676).

A retrospective chart review of 40 patients who were considered statin intolerant due to myalgia were given rosuvastatin twice weekly for at least three weeks. Thirty patients were given 5 mg while 10 were given 10 mg each week on Mondays and Thursdays. Twenty-four of the patients were also taking ezetimibe, fibrates, resins, and Chinese red rice, either alone or in combination. However, the twice-weekly rosuvastatin dosing schedule decreased total cholesterol by 19% and reduced LDL by 26%, as well as resulting in a 14% reduction in triglycerides. No significant change was noted in HDL levels. Eight patients were forced to discontinue therapy due to muscle aches, which means 80% of the patients studied were able to tolerate the therapy. The authors concluded that dose reduction contributes to decreased statin intolerance possibly by allowing muscle recovery with intermittent dosing (Gadarla et al., 2008).

Another retrospective chart review conducted by Backes et al. (2008) included 51 patients who received rosuvastatin on an alternate dosing schedule of every other day for at least one month. All of the patients had documented statin

intolerance and lipid levels drawn prior to and after treatment. The results of the study revealed significant reductions ($p < 0.001$) in triglycerides, LDL, and total cholesterol without significant changes in HDL. Furthermore, 64.9% of the patients met the NCEP ATP III LDL-C goal. Of the 51 patients, 37 were able to tolerate the alternate dosing, whereas 14 had return of myalgia symptoms and were forced to discontinue therapy. The authors theorized that alternate dosing of rosuvastatin, specifically every other day, can still result in adequate LDL reduction while avoiding therapy ending adverse effects such as myalgia. Thus, patients are better treated with alternate dosing than not being treated at all (Backes et al., 2008). Also, as stated by Backes et al. (2008), "Rosuvastatin appears to be a rational choice for markedly improving lipoprotein levels in statin-intolerant patients because of its high potency, long half-life, and lack of CYP3A4 metabolism" (p. 342). However, the authors did recognize some study limitations including the study's retrospective design, small sample size, and the fact that changes made in lifestyle modifications by individual patients were not evaluated and were not discouraged (Backes et al., 2008).

Vitamin D Supplementation

A deficiency in vitamin D can lead to myalgia, which is often the first manifestation identified (Sikka et al., 2011). Since statin intolerance is most commonly caused by myalgia, there is consideration that investigating vitamin D levels and thus correcting any deficiency can help continue statin use by resolving myalgia symptoms (Khayznikov et al., 2015). In the prospective cohort study presented by Khayznikov et al. (2015), 146 patients were assessed. Patients

included were considered statin intolerant by failing therapy of two or more agents along with low serum vitamin D levels less than 32 ng/mL. Patients with previously reported rhabdomyolysis, those taking corticosteroids, or those with any comorbidity that could lead to muscle or bone pain were excluded. The patients were given either 50,000 or 100,000 units per week of vitamin D2 to correct the deficiency. Vitamin D doses were adjusted to maintain a normal range of 50 to 80 ng/mL. Patients were then given rosuvastatin 10 to 20 mg daily three weeks after the vitamin D initiation. Statin dosing was also adjusted in an attempt to reduce LDL to meet ATP III goals. Patients completed follow-up at six months, 12 months, and 24 months (Khayznikov et al., 2015). Of the 146 patients, 88 to 95% were able to tolerate statin therapy without recurrent "myalgia, myositis, myopathy, and/or myonecrosis" with median vitamin D supplementation of 50,000 units per week (Khayznikov et al., 2015, p. 90). The authors concluded that statin intolerance due to adverse muscular effects is associated with vitamin D deficiency and can be resolved by supplementation. Additionally, vitamin D has proven to be well tolerated and its safety is not a concern (Khayznikov et al., 2015).

In another prospective cohort designed study, the goal of the authors was to determine if low serum vitamin D levels correlate to myalgia in patients on statin therapy, and if the symptoms can be reversed by adding supplementation. Of the 621 patients who had vitamin D levels drawn, 128 complained of myalgia. The vitamin D levels were low in 64%, or 82, of the patients with myalgia symptoms compared to 43% of the patients without symptoms. Of the 82 patients with myalgia, 38 had vitamin D levels below 32 ng/mL and were instructed to take

50,000 units per week of vitamin D for 12 weeks. They were allowed to continue their current statin medication, which included rosuvastatin, atorvastatin, or pravastatin (Ahmed et al., 2009). At the end of the study period, Ahmed et al. (2009) determined, "vitamin D supplementation that normalized serum vitamin D levels was concurrently associated with resolution of myalgias in 35 of 38 (92%) statin-treated patients with myalgia and low pretreatment serum vitamin D levels" (p. 15). The authors did recognize some study limitations, which included subjective reporting of myalgia symptoms by patients, lack of blinding, and not having a control group (Ahmed et al., 2009).

Glueck, Abuchaibe, and Wang (2011) also presented a prospective study where 68 patients diagnosed with hypercholesterolemia, unable to tolerate at least one statin due to myositis/myalgia, and with low serum 25 (OH) vitamin D levels less than 32 ng/mL were evaluated to identify if vitamin D deficiency correction would result in tolerance of statin therapy. Patients were given 50,000 units of vitamin D2 twice weekly for three weeks and then they continued once weekly dosing. Statin therapy was restarted after the initial three weeks of vitamin D supplementation. Patients were assessed at three months, and 91% of the patients were able to tolerate statin therapy with vitamin D supplementation (Glueck, Abuchaibe, & Wang, 2011).

A retrospective chart review of 450 patients taking simvastatin 80 mg was conducted and found that 11.1% of patients reported myalgia along with one patient, or 0.22%, who developed rhabdomyolysis. The study aimed to determine whether or not low vitamin D levels contribute to the risk of developing myalgia

while on statin therapy. Many variables were considered in this analysis including baseline laboratory values, comorbidities, medications, and demographics. The results of the study revealed a vitamin D level less than 25 ng/mL correlates to a 25% incidence in myalgia compared to 7.89% in those with levels greater than 25 ng/mL. The authors suggest that this association indicates the need for serum vitamin D monitoring and deficiency correction in order to decrease myalgia in patients on statin therapy, specifically high-dose simvastatin (Mergenhagen et al., 2014).

Another retrospective study assessed 272 patients aged 33 to 89 years of age and aimed to evaluate the possibility of a relationship between vitamin D levels and adverse muscle effects in patients on statin therapy (Eisen et al., 2014). Exclusion criteria included "conditions known to predispose to myalgia, CK elevation, or vitamin D insufficiency such as hypothyroidism, renal failure (creatinine > 1.2 mg/dl), active participation in competitive sports, known myopathy, vitamin D supplementation, acute coronary syndrome, and elevated baseline plasma CK level" (Eisen et al., 2014, p. 42-43). The analysis compared vitamin D levels and the incidence of low vitamin D levels to myalgia, CK elevation, or any reported muscular adverse effect. Variables considered included age, gender, hypertension, diabetes, smoking, CAD, and family history of premature CAD. The study did not find a statistically significant relationship between vitamin D levels and reports of myalgia, CK elevation, or any muscular adverse effect. Therefore, the authors concluded that there is no correlation between vitamin D levels and adverse muscular effects in patients on statin therapy. However, the authors did

acknowledge the fact that myalgia is a subjective finding and often hard to measure (Eisen et al., 2014).

Summary

In the alternative statin dosing studies included in this literature review, recurrent myalgia symptoms were reported in 0 to 27% of the patients. Atorvastatin faired just slightly better than rosuvastatin when considering recurrent myalgia rates. Alternative dosing appeared to be effective and led to significant LDL reduction. Some studies demonstrated a significant reduction in total cholesterol and triglycerides as well. However, the studies reviewed suggested that statin therapy given in lower doses does not have an effect on HDL. Regardless, alternative dosing appeared to be an acceptable strategy to continue statin use in patients with myalgia. Additionally, the importance of statin therapy in preventing life-threatening cardiovascular events leads to the suggestion that patients are better treated at lower doses or more infrequent doses than to not be treated at all.

Vitamin D supplementation appeared to be a bit more controversial. However, most studies reviewed did find a relationship between low vitamin D levels and statin-induced myalgia with one study reporting the correlation at 25%. Three of the studies reported that vitamin D supplementation prevented recurrent myalgia symptoms at rates of 91, 92, and 95%. The results in the studies reviewed at least warrant vitamin D level monitoring and correction of deficiency in an attempt to continue statin therapy in patients with myalgia.

The research suggested that alternative statin dosing and vitamin D supplementation have potential to allow continuation of therapy in patients with

myalgia. However, further investigation is needed to verify these results as only three of the studies reviewed were RCTs, and most of the studies had fairly small sample sizes. Furthermore, guideline development will need to be completed in order for practitioners to most effectively treat patients experiencing myalgia on statin therapy.

Learning Points

- Statin therapy is the most effective treatment for CAD proven by reduction in morbidity and mortality.
- Discontinuation of therapy is most commonly a result of myalgia symptoms.
- Alternative statin dosing, (specifically when using atorvastatin and rosuvastatin due to their longer half-life), at lower doses and/or decreased frequency has the potential to allow patients who experience therapy limiting myalgias on standard dosing to continue therapy.
- Vitamin D levels should be monitored, supplementation should be initiated to correct deficiency, and statin therapy should be rechallenged when levels normalize.
- Strategies to continue statin use in patients with myalgia should be explored by practitioners and attempts should be made to continue their use.

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