Wyoming Drug Utilization Review

Statin-Induced Myopathy and Rhabdomyolysis

Kole Thornton, PharmD Candidate 2014

Background

The American College of Cardiology (ACC) and American Heart Association (AHA) have come together and recently published new guidelines to reduce atherosclerotic cardiovascular disease (ASCVD).[1] An area of emphasis pertains to the use of statins to reduce ASCVD in four specific groups instead of using specific low-density lipoprotein cholesterol (LDL-C) treatment targets.[1] With the increase in focus on the utilization of statin therapy, it will become increasingly important to understand and appropriately manage the major adverse effects associated with these drugs.

The ACC/AHA/National Heart, Lung, and Blood Institute (NHLBI) Clinical Advisory have defined myopathy as any muscle pathology, including myalgia and rhabdomyolysis.[2] Myalgia describes muscle symptoms without a rise in creatine kinase (CK) lab values, whereas rhabdomyolysis refers to muscle symptoms with a rise in CK, usually 10 times greater than the upper limits of normal.[2]

Terminology used in trials describing statin-related muscle disease varies throughout the literature making the determination of exact incidences difficult.[3,4] The most common and serious side effects of statins are a range of myopathic symptoms from mild myalgias to fatal rhabdomyolysis.[5] About 5-10% of patients report having muscle pains while on statin therapy, though the percentage specifically attributable to statins is even lower.[6] The rarest type of myopathy encountered with statin therapy is rhabdomyolysis.[4] The incidence of rhabdomyolysis found in previous studies was 3.2 cases per 100,000 patient years.[4] The incidence of fatal rhabdomyolysis is only 1.5 cases per 10 million prescriptions.[5]

Risk Factors

Proportional increases in statin doses increase the risk of both myopathy and rhabdomyolysis.[7] Therefore, factors inhibiting the metabolism of statins or increasing plasma concentrations of statins increase these risks.[7] Examples of patient physiologic risk factors include but are not limited to: advanced age; liver or kidney impairment; and multi-system diseases such as diabetes, small body size, and untreated hypothyroidism.[7] The most common drug interactions with statins that increase the risks of myopathy and rhabdomyolysis occur with gemfibrozil, digoxin, cyclosporine, warfarin, macrolide antibiotics, and azole antifungals.[7] Niacin, HIV protease inhibitors, amiodarone, and nefazodone are also associated with an increased risk, but cases are rare.[7]

Evidence on whether a difference in risks exists with different statins is lacking.[5] Simvastatin 80 mg appears to have the highest rate of myotoxicity as compared to fluvastatin XL 80 mg which has the lowest rate, when comparing maximum doses of agents.[5] One study found that 18.2% of patients on 40 or 80 mg of simvastatin, 14.9% on 40 or 80 mg of atorvastatin, 10.9% on pravastatin 40 mg, and 5.1% on

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University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Ave
Laramie, WY 82071
307-766-6750

www.uwyo.edu/DUR

Edited by
Aimee Lewis, PharmD, MBA
Laura Miller, MS

P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on February 12, 2014. Highlights of this meeting include:

The two-year limitation on Suboxone was reviewed at the request of a provider. No changes were made to the policy.

Colcrys will be limited to 60 tablets per 30 days and a maximum duration of six months. Prior authorization will be required to exceed these limits.

Fentanyl patches will be limited to opioid-tolerant patients, defined by the label as those who have been receiving at least 60 mg of morphine, 30 mg of oral oxycodone or 8 mg of oral hydromorphone, or equianalgesic dose of another opioid, for a minimum of one week.

Trokendi XR, Fetzima, and Sovaldi will be limited to use within label. Fetzima will be non-preferred in the antidepressant category.

No evidence of a difference between Opsumit and the other agents approved for treatment of pulmonary arterial hypertension is available. Diagnosis confirmed by right heart catheterization will be required. It will be reviewed for PDL status.

No evidence of a difference between Farxiga and Invokana was identified. As with other diabetes agents, Farxiga will require a 90 day trial of metformin prior to approval and will be reviewed for PDL status.

During the closed session, Dr. Andrew Beaulieu was chosen as a new member of the P&T Committee.

All proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to March 31, 2014.

The next P&T Committee meeting will be held May 8, 2014 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

WY-DUR 2013
Retrospective Education Letters

WY-DUR focused on diabetes for the retrospective education letters during 2013. The table below lists some statistics for the 2013 mailings.

Statistics for Diabetes Retrospective Education Letters (2013)	
Number of letters sent	462
Number of responses received	173
Response Rate	37%
Specific Responses Received	
I plan to discuss with patient/healthcare providers.	69
Therapy has been modified because of this DUR.	17
This issue is not considered significant or is already resolved.	25
Please refer to Care Management.	10
Please refer to Lock-in.	1

2014 P & T
Committee Meeting Dates

Thursday, May 8

Thursday, August 14

Thursday, November 13

Meetings are held in Cheyenne at Laramie County Community College, 10 am - 1 pm. See agenda on our website (www.uwyo.edu/DUR) for room number.

80 mg fluvastatin XL developed muscle symptoms.[5] The new ACC/AHA guidelines discuss the FDA's recommendation against initiation with simvastatin 80 mg due to increased myotoxicity risks.[1]

Management of Muscle Symptoms

Two reviews have evaluated and recommended treatment options for managing patients with statin-induced myopathy.[1,5] In addition to the new ACC/AHA guidelines, the next most recent and thorough recommendations that were found were published in 2012.

Rallidis et al. recommends fully evaluating patients on statin therapy presenting with myopathy.[5] This includes both physical symptoms and lab values.[5] Depending on the severity of symptoms and lab findings there are different options available to utilize.[5] These include but are not limited to: decreasing the statin dose, discontinuing and restarting the same or a different statin at a lower dose once symptoms have resolved, and using longer acting statins on alternating days.[5] For a more fully comprehensive algorithm see the article by Rallidis et al.[5]

The ACC/AHA guidelines have a generalized and simple algorithm to managing statin myopathies which can be found in table 8 section 8 of the Stone et al. article.[1] In summary, the recommendations are to fully evaluate the patient to rule out any other causes, immediately discontinue statin therapy, and treat rhabdomyolysis if present.[1] If symptoms are only mild to moderate, the options revolve around identifying what caused the symptoms to determine if a lower dose of the same statin or different statin should be utilized.[1]

The utilization of Coenzyme Q-10 (CoQ10) for relieving pain associated with statin-induced myopathy is a topic of interest. One of the theories behind statin myopathy is a CoQ10 deficiency.[5] CoQ10 plays a role in proper cellular oxidative phosphorylation and low levels can result in mitochondrial dysfunction.[5] There is conflicting evidence on whether the use of CoQ10 directly affects muscle pain or whether placebo effect plays a role.[8] Serum CoQ10 levels drop with statin therapy, however levels in myocytes are not usually decreased.[5] The efficacy data for CoQ10 in statin myopathy remains unclear, however the fact that there are no known risks with CoQ10 would advocate the recommendation of a trial of 200 mg daily of CoQ10.[5]

Conclusion

Treatment with statins for specified groups has come to the forefront of healthcare with the new ACC/AHA guidelines. It is important that proper monitoring and management of adverse effects occur to ensure the best utilization of these drugs for improved patient outcomes. The most common and serious side effects with statins are myopathic symptoms. There are multiple options for dealing with this side effect, some of which include lower doses of statins, using a different statin or regimen, and utilizing CoQ10 for symptom relief. As with most patient care, no scenario is the same and patient characteristics must be taken into account when selecting the best option.

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University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Avenue
Laramie, WY 82071

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