Management of statin-related muscle pain: Clinical strategies in patients at high cardiovascular risk

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ABSTRACT

This book chapter examines the relationship between statin use and statin-induced myalgia, emphasizing the importance of effective management strategies. It aims to identify the main symptoms, evaluate risk factors, mechanism of action and especially explore alternative treatments, including the association of statins with vitamin D. The methodology involved a descriptive and qualitative literature review focusing on databases such as Scielo, Google Scholar and PubMed, from 1996 to 2024. The results show the need for personalized approaches in treatment, considering individual variability in response to medication. It is concluded that in-depth understanding and careful management are crucial to improve treatment adherence and quality of life for patients.

Keywords: Adverse effects of statins, Statin-induced myopathy, Management of statin-related myalgia, Interaction of vitamin D with statins.

INTRODUCTION

Statins are the main class of drugs used to lower serum cholesterol concentration for primary and secondary prevention of cardiovascular disease. (Rosenson et al., 2024). Although they are generally well accepted, it is important to be aware of possible side effects, such as muscle aches or weakness, cramps, and rarely rhabdomyolysis. Statin-associated myopathy is one of the most common adverse effects observed, and is usually reversible with discontinuation or dose reduction (Iwere, R., et al. 2015).

According to Rallidis et al. (2012), muscle pain, which is usually symmetrical and affects proximal muscles, is the most frequent manifestation of statin-related myopathy, usually occurring without elevation in creatinine kinase (CK) levels. It is important to highlight that the pathophysiological mechanism behind this condition is still unknown and considered multifactorial. In clinical practice, about one-third of patients using statins have muscle complaints that can be exacerbated by physical exercise (PEBMED, 2018). In addition, risk factors include drug interactions and patient characteristics. In this context, ensuring the uninterrupted progress of treatment depends heavily on the effective management of these pains.

This study is a vital study due to the increasing use of statins and the associated incidence of myopathy, affecting treatment adherence and quality of life of patients, seeking to identify specific symptoms, explore personalized management options, and investigate the potential role of vitamin D in the prevention of statin-induced myopathy, contributing to more effective and safer clinical strategies.

GENERAL OBJECTIVE

To identify effective clinical strategies in the management of muscle pain in patients treated with statins.

SPECIFIC OBJECTIVES

The specific goals outlined to achieve this goal include: identifying the main symptoms of statin-induced myopathy, such as muscle pain, weakness, and cramps; to evaluate the risk factors associated with the occurrence of muscle pain in patients treated with statins; review diagnostic and monitoring strategies for early detection of drug-related myopathy; explore therapeutic alternatives for the management of muscle pain, including dose adjustment, statin change, or use of adjuvants; and to investigate the relationship between serum vitamin D levels and the development of statin-induced myopathy, evaluating statin-induced vitamin replacement as a possible intervention. These specific objectives will serve as a solid foundation for the study and will contribute significantly to

improving the diagnosis and alternative management of statin-related myalgia, offering new perspectives for effective and personalized treatments for patients.

METHODOLOGY

The present work consists of a literature review that sought to address results found in research on the theme in question, either in a comprehensive, orderly or systematic way. Focal points include symptomatology, risk factors, diagnostic methods, alternative therapies, and the impact of vitamin D.

The inclusion criteria for this view include specifically investigating statin-induced myopathy, diagnostic and monitoring techniques, therapeutic interventions, and the correlation between vitamin D. Any studies that do not directly address these aspects or focus on other statin-related complications will be excluded.

To carry out the search, several electronic databases will be used, such as Google Scholar, Scielo and PubMed. The keywords chosen will align with the specific objectives of the study and will include terms such as "Statin Adverse Effects," "Statin-Induced Myopathy," "Management of Statin-Related Myalgia," "Vitamin D Interaction with Statins," and other pertinent terms.

The study selection process will follow a qualitative and descriptive methodology. Initially, abstracts that seem to meet the inclusion criteria will be identified. Subsequently, the full articles will undergo a thorough review to assess their adequacy and relevance to the objectives of the study. Throughout the data extraction process, information pertaining to the occurrence of statin-induced myopathy will be collected, including documented symptoms, diagnostic approaches, and the effectiveness of various treatment strategies.

When assessing the quality of studies, their methodological rigor, clinical significance, and timeliness will be carefully considered. It is important to note that this review will only cover articles published from 1996 to 2024, which may result in the exclusion of previous research, but ensures that the information analyzed is current and relevant. In addition, the analysis will be limited by the specific terms and languages used in the searches, potentially leading to the omission of pertinent studies that do not align with the designated keywords.

RESULTS AND DISCUSSIONS

According to Paschoalino and Toazza (year), statins, a hydroxymethylglutaryl (HMG) CoA reductase inhibitor drug, have proven to be effective in reducing the risk of cardiovascular events such as heart attacks and strokes, mainly reducing cholesterol levels in patients with dyslipidemia. These drugs are recommended for patients with cardiovascular risk factors and have been shown to

be effective in both primary and secondary prevention of these events. It is crucial for patients to adhere to their statin treatment regimen to achieve optimal therapeutic outcomes.

Available statins include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin, all of which occupy a portion of the HMG CoA binding site, blocking access of this substrate to the enzyme's active site (Istvan ES, et al. 2001), resulting in an increased rate of hepatic Low-Density Lipoprotein (LDL) receptor cycling (Ness GC et al. 1996). This means that under the influence of statins, LDL receptors in the liver are reused at a higher rate, thus allowing for more efficient removal of LDL, or "bad cholesterol," from the blood.

Normally, statins by blocking HMG CoA reductase, a specific pathway in the liver, which is essential for the production of cholesterol, also affects the production of certain important substances called geranyl pyrophosphate and farneyl pyrophosphate, which play a crucial role in regulating vital functions in muscle cells. When the production of these substances is reduced, it can result in changes in muscle function and communication, thus leading to the occurrence of pain.

Symptoms of statin-induced myalgia and myopathy usually manifest as muscle weakness and/or pain that symmetrically affects proximal muscles. Patients may also experience muscle tenderness and functional limitations, such as difficulty performing tasks such as raising the arms above the head, getting up from a sitting position, or climbing stairs. These symptoms are often described by patients as fatigue or tiredness. In some cases, the discomfort may be asymmetrical. Additional symptoms reported include cramping (including nocturnal cramps), stiffness, and pain in the tendons. It is noteworthy that not all patients with these symptoms will have elevated serum creatine kinase (CK) levels.

According to GELATTI (2016), risk factors related to myalgia secondary to the use of statins include advanced age (> 80 years), female gender, low body mass index, chronic systemic disease, use of multiple drugs, alcohol use, and strenuous physical exercise.

In addition, people's response to statins may be influenced by their individual genetics, as some patients have genetic variations that make them more likely to develop muscle soreness when using statins. This may be related to how their bodies absorb and process the drug.

According to Khan (2022), the clinical evaluation of statin-associated myalgia involves distinguishing symptoms directly attributable to statin use from other symptoms that cause muscle pain. This includes a detailed review of the patient's medical history and symptoms, consideration of other potential causes of muscle pain, and the use of objective measures such as creatine kinase levels. Trials in which patients switch between statins and placebo are particularly useful in determining whether symptoms are actually related to statins.

Smith CC (2003) stated that, despite the increased risk of myopathy associated with statin therapy, routine monitoring of serum creatine kinase (CK) levels is not recommended based on a

retrospective study of more than 1,000 patients in primary care practices. There were no obviously abnormal CK values, and only two moderately abnormal CK values may be related to statin use. However, it is useful to obtain baseline serum CK before initiating statin therapy as a reference at symptom onset.

According to a study by Alonso R (2019), to avoid premature discontinuation of statins due to muscle pain in high-risk patients, it is critical to emphasize the proven cardiovascular benefits of statins in patients. Lifestyle changes, such as diet modification, exercise, and smoking cessation, play a key role in lowering cholesterol levels and improving other cardiovascular risk factors, thereby helping to reduce it. Several statin-based strategies have been proposed to control muscle symptoms, such as switching to another statin, reducing the dose (withdrawal) or frequency (intermittent dosing), or repeating the same statin therapy. If the new approach is well tolerated, the dose can be increased gradually to achieve LDL-C targets with little or no muscle discomfort. For patients who cannot tolerate daily statins, dosing every other day or twice a week is a viable option. Rosuvastatin and atorvastatin have a longer half-life and can therefore be used part-time. For patients who reported muscle symptoms to their doctors, the most common recommendation was to switch to another statin.

If statins are not well tolerated, alternative cholesterol-lowering agents, alone or in combination with the maximum tolerated dose of statin, are recommended to achieve LDL-C targets. Ezetimibe is preferred when added to lower doses of statins or alone, and can reduce LDL-C by 20% and is generally well tolerated.

If ezetimibe is insufficient to meet LDL-C goals, consider adding a fibrate. Fibrates reduce LDL-C levels by approximately 15%, and their cardiovascular benefits have been demonstrated in an analysis of randomized controlled trials in patients with hypertriglyceridemia. However, because of the potential for myopathy, the use of gemfibrozil with statins should be avoided. In this context, fibrates such as fenofibrate are preferred as they have a lower risk of adverse interactions.

In addition, Hou Q (2022) showed that vitamin D (25OHD) levels were significantly lower in patients with statin-associated myopathy compared to patients without myopathy and patients with vitamin D deficiency and muscle intolerance to statins, vitamin D supplementation can increase the statin tolerance rate to 89%. Taken at first glance, these results suggest an association between low 25OHD levels and statin-induced myopathy and evidence that vitamin D supplementation may help improve statin-related muscle intolerance in patients with hypovitaminosis D. However, these results are mixed and more research is needed to confirm this association and better understand the underlying mechanisms.

FINAL THOUGHTS

This study highlights risk factors for statin-induced myalgia, which include older age, female gender, low body mass index, and strenuous exercise. In addition, it depicts alternative management that involves adjusting the dose of statins or switching them to types that are less likely to cause myalgia. In addition, alternate-day administration is a viable option. It was evidenced that the combination with ezetimibe was also shown to be effective, offering a further reduction in LDL-C levels with fewer muscle adverse effects. In addition, research points out that vitamin D supplementation may be beneficial for patients with vitamin D deficiency and muscle intolerance to statins. Future research should explore more individualized strategies for the management of statin-induced myalgia, considering genetic and metabolic variations in patients. It is also important to further investigate the relationship between vitamin D deficiency and statin tolerance. In this sense, the search for predictive markers of statin intolerance and the development of new lipid-lowering agents with a lower incidence of muscle side effects are other promising fields. Therefore, this research may lead to a better understanding and management of statin-related myalgia, expanding therapeutic options and improving patients' quality of life.

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