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REVIEW ARTICLE

Statin-related myotoxicity

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Abstract Statin therapy has a very important role in decreasing cardiovascular risk, and treatment non-compliance may therefore be a concern in high cardiovascular risk patients. Myotoxicity is a frequent side effect of statin therapy and one of the main causes of statin discontinuation, which limits effective treatment of patients at risk of or with cardiovascular disease. Because of the high proportion of patients on statin treatment and the frequency of statin-related myotoxicity, this is a subject of concern in clinical practice. However, statin-related myotoxicity is probably underestimated because there is not a gold standard definition, and its diagnosis is challenging. Moreover, information about pathophysiology and optimal therapeutic options is scarce. Therefore, this paper reviews the knowledge about the definition, pathophysiology and predisposing conditions, diagnosis and management of statin-related myotoxicity, and provides a practical scheme for its management in clinical practice.

PALABRAS CLAVE
Estatinas;
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Intolerancia a estatinas;
Miotoxicidad;
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Miotoxicidad por estatinas

Resumen El tratamiento con estatinas tiene un papel fundamental en la reducción del riesgo cardiovascular, y la falta de adherencia al mismo es motivo de preocupación en los pacientes con alto riesgo. La miotoxicidad es un efecto secundario frecuente y una de las principales causas de interrupción de las estatinas, lo que limita el tratamiento eficaz de los pacientes con riesgo de enfermedad cardiovascular. Considerando la elevada proporción de pacientes en tratamiento con estatinas, y la frecuencia de miotoxicidad asociada, este es un tema relevante en la práctica clínica. Sin embargo, la miotoxicidad por las estatinas está probablemente subestimada debido a que no hay una definición bien establecida y su diagnóstico resulta difícil.

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Además, la información sobre la fisiopatología y las opciones terapéuticas óptimas es escasa. En este artículo revisamos la definición, fisiopatología y condiciones predisponentes, diagnóstico y tratamiento de la miotoxicidad por las estatinas, y proponemos un esquema práctico para su manejo.

Introduction

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are the most widely used lipid-lowering drugs. Their value in reducing the risk of atherosclerotic diseases and their good patient acceptance make them one of the most widely prescribed drug classes.[1,2] Despite their safety, a significant proportion of patients report adverse effects. Muscular toxicity is a well-recognized side effect of statins, and 7–29% of patients experience statin-associated muscle symptoms according to registries.[3,4] Moreover, statin-associated muscle symptoms are one of the main reasons for statin therapy non-adherence or discontinuation.[4,5] In a retrospective cohort study, 59.2% of patients with documented statin-associated events discontinued statins at least temporarily, which may have a marked impact on the cardiovascular benefits of statin therapy.[6–8] Thus, considering the high number of patients on statin therapy and the possibility that side effects cause treatment discontinuation in high cardiovascular risk patients, statin-related myotoxicity is a relevant problem in daily clinical practice. However, muscle toxicity of statins has been largely neglected until recently and there is no gold standard diagnostic test, its pathophysiology remains unclear, and information about the optimal therapeutic option is scarce.[9,10] This article reviews and discusses the information available on the pathophysiology, diagnosis, and management of statin-related myotoxicity, and provides a practical scheme for its management in clinical practice.

Definition and epidemiology

There is not a gold standard definition of statin-related myotoxicity, but multiple definitions have been provided by different organizations such as the American College of Cardiology (ACC)/American Heart association (AHA), the National Heart, Lung and Blood Institute (NHLBI), the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the European Atherosclerosis Society (EAS). Traditionally, statin-related myotoxicity was referred to as statin-associated myopathy, but this term included several distinct conditions with different outcomes and particular requirements for management. The 2014 National Lipid Association Statin Muscle Safety Task Force proposed that muscle-related adverse effects of statins consisted of a range of 5 categories[9]:

- Myalgia: muscle discomfort similar to a viral syndrome (''flue-like'' symptoms) including muscle aches, soreness, stiffness, tenderness, or cramps (with or soon after exercise, not nocturnal), with a normal creatine kinase (CK) level.
- Myopathy: muscle weakness (not related with pain), without association with CK level.
- Myositis: muscle inflammation.
- Myonecrosis: elevation of muscle enzymes compared with baseline CK levels or upper limit of normal adjusted for age, sex and race. Myonecrosis may be divided into 3 different degrees according to CK elevation: mild (if there is a three-fold to ten-fold CK elevation), moderate (ten-fold to fifty-fold elevation) and severe (fifty-fold or greater elevation).
- Clinical rhabdomyolysis: myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of at least 0.5 mg/dL).

This spectrum does not represent a continuum of increasingly severe myopathic manifestations. Different definitions have been used by different societies and studies, which should be taken into account when results from different reports are compared.[11]

Data on the incidence of statin-related myotoxicity has been collected from randomized clinical trials (RCTs) and observational studies. Large clinical trials have reported statin-induced muscular side effects in up to 12.7% of patients (usually <1.5–5%), while observational studies have shown a significantly higher incidence (7.9–30%). Despite these differences, both types of studies have shown that muscle side effects are common, with myalgia being most prevalent, while rhabdomyolysis is a rare occurrence.[3,4,12–18] The Effects of Statins on Skeletal Muscle Function and Performance (STOMP) study, specifically designed to assess the impact of high-dose statin therapy for 6 months in healthy, statin-naive subjects, revealed that atorvastatin 80 mg significantly increased the frequency of myalgia as compared to placebo (9.4% versus 4.6%).[13] The reported differences may be due to scarce assessment of muscle complaints in RCTs, exclusion of patients with risk factors or previous family or personal history of muscular side effects induced by lipid-lowering drugs, and exclusion of patients with muscle complaints during the pre-randomization, unblinded run-in phase.[9,11] All these factors can contribute to a lower incidence rate of muscle side effects in RCTs, and may be assumed to result in an underestimation of the actual incidence in clinical practice. On other hand, both RCTs and observational studies may overestimate this incidence by attributing to statins muscle complaints due to other causes.[9] Accordingly, 90% of patients reporting