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LETTERS TO THE EDITOR
Bilingual edition English/Spanish

Atorvastatin induced rhabdomyolysis: Utility of determining genetic polymorphisms

Rabdomiólisis por atorvastatina: Utilidad de la determinación de los polimorfismos genéticos

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Dear Editor-in-Chief,

Cases of statin-induced rhabdomyolysis amount to 1-3 per 100,000 patients/year[1].

Clinicians are well aware of the importance of liver insufficiency and/or drug-drug interactions when it comes to prescribing statins. It is less known, however, that inter-individual variability, i.e., genetic polymorphisms, at the level of CYP3A4, CYP2C9 and SLCO1B1 (OATP1B1 codifying gene) could affect the effectiveness and the safety of these drugs[2]. The c.521T > C (rs4149056) polymorphism has been associated with high statin plasma concentrations, increasing the patients' risk of developing myopathy[3].

We hereby present the case of an 84-year-old hypertensive yet functionally independent patient (Barthel score: 100; Lawton score: 8) with no cognitive impairment who was hospitalized for non-ST elevation acute coronary syndrome (NSTE-ACS) with lesions in two vessels. A percutaneous coronary intervention (PCI) was performed with implantation of two stents. After discharge, she was treated with clopidogrel 75 mg, acetylsalicylic acid 100 mg, pantoprazole 20 mg, ramipril 5 mg, bisoprolol 2.5 mg, zolpidem 10 mg and atorvastatin 80 mg. At 25 days, she had to be readmitted for disabling pain in her right gluteus, which irradiated to the ipsilateral leg. Despite being treated by her primary care physician with intramuscular betamethasone, gabapentin and oxycodone, her symptoms worsened making walking impossible and standing very painful. An x-ray study was carried out, which helped rule out an acute fracture. Blood tests carried out on admission showed creatinine levels at 1.32 mg/dL, GOT 991 IU/L, ALT 477 IU/L and CK 28,290 IU/L. Statins were discontinued, fluid therapy and analgesia were initiated, and an MRi was requested (which never got performed because the patient died). Forty-eight hours later, the patient's clinical situation worsened, with hemodynamic instability and severe abdominal pain. An abdominal CT-scan was performed, with no conclusive findings. Intensive treatment was applied in a general ward, with unfavorable evolution and exitus.

The genetic polymorphism present was determined, which expressed normal activity for the CYP2C9/3A4 and UGT1A1 genes, and intermediate activity for SLCO1B1 1A*/5 [SNP V174A (rs4149056)].

The potential connection between rhabdomyolysis and atorvastatin was evaluated by applying Naranjo's algorithm and considering the first adverse reaction as the definitive one. Results were reported to the Spanish Pharmacovigilance System for Drugs for Human Use.

Of all the patients' characteristics, the ones that increased the risk of developing myopathy were advanced age, female sex, high statin dose, prescription of a lipophilic statin (atorvastatin)[4] and presence of the SLCO1B1 intermediate metabolizer, whose metabolizing activity, estimated at 35% of the normal value, resulted in increased atorvastatin plasma concentrations.

None of the patient's concomitant medications were associated to an increased risk of rhabdomyolysis. A review of potential interactions revealed that concomitant drugs were independent with respect to genotypes SLCO1B1 c.521T> C ,CYP2C9/3A4 and UGT1A1.

The effectiveness of statins following myocardial infarction in persons over 80 years of age remains a moot point. Statins are recommended if the patient's life expectancy is above three years and if they present with few comorbidities, good functional capacity, and an absence of significant cognitive impairment. Monitoring for potential signs of myopathy is essential[5]. Further studies will be necessary to determine whether an assessment of the patient's frailty and/or an adjustment of the prescribed dose of statins may reduce statin-associated morbidity and/or mortality in the elderly.

As far as statins are concerned, it will be essential going forward to individualize the dose of statins, taking into consideration the genetic poly-

morphisms found in our patients so as to identify those at risk of developing myopathy or rhabdomyolysis and adjust the statin dose administered, select the type of statin to be prescribed according to the patient's metabolism, or rule out the use of statins depending on the phenotype identified.

Given the high number of patients treated with intensive statin doses, it is paramount to determine which of them would benefit the most from phenotype determination. We believe such a determination could be particularly useful in patients with a family history of cardiovascular events or adverse reactions to statins. This approach, combined with close multidisciplinary collaboration, could help increase the effectiveness and safety of the treatments prescribed to our patients.

The relevant informed consent was obtained prior to publishing this letter.

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