Statins and muscle rupture

Introduction

Statins inhibit the enzyme 3-hydroxy-methylglutaryl-co-enzyme A-reductase (HMG-CoA-reductase), which plays an essential role in the synthesis of cholesterol by catalysing the conversion from HMG-CoA to mevalonate [1]. Statins are indicated for *hypercholesterolemia*. They are effective in both the primary and the secondary prevention of ischemic heart diseases and stroke prevention [2-4]. Over the past decades, several statins have been granted marketing authorization in the Netherlands, including simvastatin (Zocor®), pravastatin (Selektine®), fluvastatin (Lescol®), atorvastatin (Lipitor®), rosuvastatin (Crestor®) and more recently pitavastatin (Vezepra®, Livazo®) [1].
One of the most important and well-known ADRs of statins are the musculoskeletal ADRs; including myalgia, muscle cramp, myopathy, myositis and rhabdomyolysis [1,5-11]. It is important to differentiate myalgia from myopathy and myositis. Although myopathy and myositis may cause myalgia, most individuals with myalgia have neither [12]. The risk for myopathy is increased by higher doses, predisposing factors (renal failure, hypothyroidism, personal or family history of hereditary muscular disorders, history of muscular toxicity caused by a statin or fibrate, history of liver disease and/or alcohol abuse, female sex, and age >65 years) and in combination with other drugs, in particular fibrates [1].

A muscle rupture is a contraction-induced injury in which muscle fibres tear. It mostly occurs as a result of a powerful eccentric contraction or overstretching of the muscle and is therefore a typical injury during explosive movements, such as sprinting, lunging or jumping [13]. Historically, acute muscle injuries have been classified as strains (grade I), partial tears (grade II) and complete tears (grade III) [14]. Spontaneous muscle ruptures that occur without intense muscle contraction are very rare.

Reports

The Netherlands Pharmacovigilance Centre Lareb received 11 reports on muscle rupture associated with the use of statins, in the period from 22 February 2006 until 12 January 2014. The reports are listed in Table 1.

Table 1. Reports of muscle rupture associated with the use of statins.

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A, 166606, M, 61-70 years, physician	simvastatin, 1dd 40mg, secondary prevention CVA	baclofen, clopidogrel, lisinopril, valsartan, tamsulosin, hydrochloro-thiazide, venlafaxine, nifedipine	muscle rupture	15 month, withdrawn, recovering
B, 158137, F, 61-70 years, physician	simvastatin, 1dd 40mg, hypercholesterolaemia	salmeterol/fluticasone, calcium carbonate/colecalciferol, fluticasone, zolpidem, pramipexole, omeprazole,	muscle rupture	8 months, withdrawn, unknown

		oxazepam, ibuprofen		
C, 154672, F, 51-60 years, physician	rosuvastatin, 1dd 10mg, hypercholesterolaemia	pramipexole	muscle rupture	7 months, withdrawn, recovering
D, 152410, M, 41-50 years, consumer	atorvastatin, 1dd 20mg, cardiovascular disorder	metoprolol	muscle rupture, back pain, myalgia, liver enzyme abnormal, stools abnormal	1 month, withdrawn, recovered
E, 115957, M, 61-70 years, pharmacist	atorvastatin, 1dd 10mg, cardiac arrhythmia	phenprocoumon, digoxin, metoprolol	muscle rupture	5 years, continued, recovered
F, 128372, F, 71 years and older, consumer	pravastatin, 1dd 20mg, hypertension	ezetimib	muscle rupture, myalgia	4 months, withdrawn, unknown
G, 86755, M, 51-60 years, nurse	pravastatin, 1dd 10mg, hypercholesterolaemia		muscle rupture, tendon rupture	within 1 month, withdrawn, recovered with sequel
H, 83259, M, 61-70 years, physician	rosuvastatin, 1dd 10mg, hypercholesterolaemia ofloxacine, 1dd 400mg, prostatitis	omeprazole, metoprolol, ramipril, lercanidipine, hydrochloro-thiazide/valsartan, povidone	muscle rupture, drug interaction	2 years / 3 days, continued / withdrawn, unknown
I, 70663, M, physician	fluvastatin 20mg		muscle rupture	7 years, withdrawn, unknown
J, 58917, M, 41-50 years, specialist doctor	rosuvastatin 1dd 40mg, hypercholesterolaemia		muscle rupture	months, withdrawn, recovered
K, 55786, M, 61-70 years, specialist doctor	fluvastatin, hypercholesterolaemia, diltiazem, coronary artery disease	acetylsalicylic acid, quinapril	muscle rupture, tendon rupture	5 years, withdrawn, unknown

Case A describes a patient with first a rupture of his left biceps and second a rupture of his right biceps. The patient was a highly trained athlete in the period before the ruptures occurred.
Case B describes a partial rupture of the biceps muscle.
Case C describes a rupture of the calf muscle. Within several months the patient experienced three spontaneous muscle ruptures of the calf in both legs. The muscle rupture did not occur during exercise or lunging, but during normal daily activities. The earlier muscle ruptures were misdiagnosed as thrombophlebitis. This report involves the third rupture, which was a rupture of the medial head of the gastrocnemius muscle. This was confirmed by a physiotherapist. In the period of the occurrence of the first muscle rupture, creatine kinase (CK) level was 123 U/L. Four months later the CK level was 190 U/L. Again one month later, at the moment of the third muscle rupture, CK level was 156 U/L. CK levels after the withdrawal of rosuvastatin were unknown.

Case D describes a muscle rupture during exercise. During earlier treatment with simvastatin the patient was suffering from musculoskeletal pain and had increased liver enzymes.
Case E describes a rupture of the hamstring. The patient twice experienced a hamstring injury in the past. It is unknown if the patient was treated with statins during the occurrence of the previous hamstring injuries.
Case F describes a spontaneous rupture of the right biceps and rupture of a knee ligament.
Case G describes a patient who was treated with atorvastatin prior to the treatment with pravastatin. Case H describes a rupture of the right calf muscle that occurred spontaneously while standing. In this case it cannot ruled out that the muscle rupture is caused by the treatment with ofloxacine.
Case I describes that the deterioration continued after withdrawal of fluvastatin. Later the situation stabilised.
Case J describes an obese patient (BMI: 32.8 kg/m^2) who experienced three muscle ruptures during treatment with rosuvastatin. The patient suffered from myalgia during earlier treatment with atorvastatin. The patient was physically active. At the moment atorvastatin was withdrawn and rosuvastatin was started CK levels were 212 U/L. At the moment of the first muscle rupture the CK level was 310 U/L. In the month that rosuvastatin was withdrawn the CK level was 121 U/L.
Case K describes a patient with a rupture of muscles and tendons of both biceps and both quadriceps. CK levels were 88 U/L, which is within the normal range of 20-200 U/L for men, nine months after the withdrawal of fluvastatin.

In 2 cases (B and C) the reporter explicitly stated that the rupture was not a rupture of the tendon. In two cases (D and J) exercise could have played a role in the occurrence of the muscle rupture. In five cases (B, E, G, I and K) it was unknown if the muscle rupture occurred during exercise or during normal daily activities. In four cases (A, C, F and H) it was mentioned that the muscle rupture occurred spontaneously during normal daily activities. It is remarkable that only two reports (D and F) mentioned myalgia as an ADR.

Other sources of information

SmPC

The SmPCs of statins available on the Dutch market do not mention muscle rupture as an ADR [5-9]. However they do mention, except for fluvastatin [7] and pitavastatin [10,11], tendon rupture as a possible ADR [5,6,8,9].
The US SPCs of statins available on the US market do not mention muscle rupture as a possible ADR [15-21]. Only the US SmPC of atorvastatin mentions tendon rupture as a possible ADR [16].

Literature

Myotoxicity can occur during treatment with statins. Possible ADRs that are described in literature are myalgia, muscle cramps, myositis, rhabdomyolysis and increased serum levels of creatine kinase. Tendon ruptures are also described [22,23].
Mansi et al. reported for the first time that statin use was associated with increased risk of dislocation/strain/sprain and maybe osteoarthritis [22]. An association between treatment with statins and muscle rupture has not been described in literature.

Databases

Table 2. Total reports of muscle rupture associated with statins in the databases of Lareb [24], WHO [25] and EMA [26].

Drug	Number of reports	Combined ROR (95% CI)
statins	Lareb: 11	24.1 (10.6 – 54.6)
	WHO: 107	11.7 (9.5 – 14.4)
	Eudravigilance: 118	13.1 (10.7 – 16.0)

Prescription data

Table 3. Total number of patients using statins in the Netherlands between 2009 and 2013 [27].

	2009	2010	2011	2012	2013
statines	1,507,000	1,594,000	1,662,000	1,751,000	1,827,000

Mechanism

It is plausible that myotoxicity can predispose muscles to tear. Many hypothesis have been proposed to explain the myotoxicity caused by statin use. Statins can weaken the integrity of skeletal muscles by reducing the cholesterol content in cell membranes. Another theory explains the myotoxicity by a reduction in the availability of the isoprenoid cometabolites farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (G-PP), causing a reduction in the prenylation of small guanosine triphosphate-binding proteins, such as Rac, Rho, and Ras, which is thought to result in apoptosis of muscle cells. Statins catalyzes the synthesis of mevalonate. Mevalonate is an important precursor of cholesterol, but also of ubiquinone (coenzyme Q), dolichol, and isopentenyl adenosine. Deficiencies in these products may affect the membrane of the myocyte adversely, predisposing the cell to myotoxic consequences. In addition, statins induce a sustained increase in cytosolic Ca^{2+} levels, which could lead to muscle dysfunction and dysregulation. Statin use can also lead to secondary carnitine deficiency that clinically may manifest as myositis and/or myalgia. Some evidence suggests that statins can inhibit lactic acid efflux from myocytes and thereby induce damage to muscle cells. Alterations of protein synthesis and protein degradation have also been implicated in statin-induced myotoxicity [28].

Draeger et al. performed a study to further investigate the mechanism that mediated statin-induced skeletal muscle damage. Skeletal muscle biopsies from statin users who were asymptomatic were examined and compared with skeletal muscle biopsies from non-statin-users, using both electron microscopy and biochemical approaches. The study shows a clear evidence of skeletal muscle damage in statin-users, with a characteristic pattern that includes breakdown of the T-tubular system and subsarcolemmal rupture. These characteristic structural abnormalities were reproduced by extraction of cholesterol from skeletal muscle fibers in vitro. The authors hypothesize that statin-induced cholesterol lowering contributes to myocyte damage, regardless of whether the patient is symptomatic. This could explain why only two casus describe myalgia as an ADR. The sophisticated membrane architecture with its unique lipid/protein segregation of the skeletal muscle accounts for the vulnerability of skeletal muscle sarcolemma [29].

Discussion and conclusion

Lareb received 11 reports of muscle rupture associated with the use of statins. The association showed strong significant disproportionality in the Lareb, WHO and Eudravigilance database. Despite that the association has not been described in

literature, it is plausible that statin-induced myotoxicity can predispose muscles to tear. Myotoxicity is a well-known ADR of statins [22]. Our data suggests that statin-induced muscle rupture can occur without intense muscle contraction and without the presence of myalgia. The association of muscle rupture with the use of statins is a new signal.

- Further investigation of the marketing authorization holder and other national centres is needed to evaluate the signal

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This signal has been raised on October 2014. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbgmeb.nl/cbg/en/default.htm