Incidence of skeletal muscle disorders after statins' treatment: Consequences in clinical and EMG picture

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Abstract

OBJECTIVES: The goal of this clinical trial was to determine the incidence of undesirable side effects, and to ascertain any occurrence of genetic polymorphisms.
MATERIAL AND METHODS: Clinically, we looked for manifestations of a benign myositis and of serious rhabdomyolysis. We observed a group 198 patients treated with statins, primarially fluvastatin and rosuvastatin. There were 126 (mean age = 58.3±4.1; male 91, mean age = 57.4±5.9; female 35, mean age = 60.5±6.5) patients in a subgroup where we administered rosuvastatin. Undesirable muscular signs and symptoms were present in 32 patients (25.39%). In 11 (8.73% of the total 126) CK level increased maximally to 4 times ULN, in 6 (4.7%) statins were excluded because of very intense subjective suffering. CK levels 2–5 times ULN were present in 9 (7.14%). CK blood levels over 10 times ULN or higher indicated statins exclusion in 2 (1.58%). Increased levels of the further muscular enzyme AST by 5 times ULN were present in 16 (12.69%), up to 10 times ULN in 2 (1.58%), and over 10 times ULN also in 2 (1.58%).
RESULTS: We observed rhabdomyolysis in 6 patients (3.03% of the total 198 patients group) using other types of statins (three of them undergo chronic hemodialysis). In this group we performed molecular-genetic analysis of the following proteins relating to statin myopathy: SLCO1B1(388AA/AG-521TT) – (discovered polymorphism in 1 patient), further cytochroms Cyp 2C9 (in 1 patient), 2C8 (in 1 patient), Cyp SA/4 (non discovered positivity) and finally UGT1A1*2B (discovered in 2 patients).
CONCLUSIONS: In the group of patients treated by rosuvastatin, we discovered not one case of rhabdomyolysis. In each patient with rhabdomyolysis (brown urine discoloration, mal-odorous urine, painful muscle cramps, muscle weakness, fatigue) at least one polymorphism of "statins´ genes" was present.

ORIGINAL ARTICLE

INTRODUCTION

Statins lower cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the biosynthesis of cholesterol. However, severe adverse events, including myalgias and rhabdomyolysis, have been reported with statin treatment. Different mechanisms have been proposed to explain statin-induced myopathy, including reduction of mevalonate pathway products, induction of apoptosis, mitochondrial dysfunction, and genetic predisposition. A decrease in coenzyme Q_{10} (CoQ), a product of the mevalonate pathway, could contribute to statin induced myopathy. EMG, and biochemical features of statin-induced myopathy, the inter-relationship between statins and the concentration of CK (Creatine Kinase) and isoemzymes in plasma and whether there is a role for supplementation with CoQ to attenuate statin-induced myopathy are discussed in (Sonoda *et al.* 1994; Meriggioli *et al.* 2001; Nakahara *et al.* 1998, Littlefield *et al.* 2014).

Statins are associated with a range of muscle problems, but they are not common, and nearly always reversible on statin withdrawal. In randomized controlled trials the frequency and severity of these problems did not differ between treated and placebo groups. As a rough guide, we can say that for every 100,000 patients treated for one year, four will suffer from rhabdomyolysis, and 33 will suffer from myositis, but these rates do not differ significantly from those observed in the placebo group (Thompson *et al.* 2003; Tomlinson & Mangione 2005). Withdrawal of statins increasingly improves clinical signs and symptoms to the final normalization into the cases with early stopping of statin treatment but the following question has to be answered: Is withdrawal of a placebo in the most placebo induced rhabdomyolysis cases effective? Our personal experience is, probably not. Lipid lowering drugs are used worldwide to control dyslipidemias. The muscle disorder associated with them are coined cholesterol-lowering agents myopathy (CLAM) (Thompson *et al.* 2003). The annual incidence of rhabdomyolysis in patients taking statins is 1.5–4 per 100 000 persons (London *et al.* 1991; Sathasivan & Lecky 2008). Statin-induced apoptosis of cardiac myocytes in some pathological states may attenuate cardiac hypertrophy and remodeling (Demyanets *et al.* 2006.). However, statin-induced apoptosis of healthy skeletal myocytes may be a contributing factor causing myopathy (Johnson *et al*. 1998; Matzno *et al.* 2005; Mutoh *et al.* 1999; Sacher *et al.* 2005). The discrepancy between clinical trials and clinical experience reduces confidence in lipid-lowering therapy and contributes to its under use (Fernandez *et al.* 2011).

Fig. 1. Urine of a person with rhabdomyolysis and the characteristic brown urine discoloration as a result of myoglobinuria and odor like chicken liver (private experience).

Because of the discovered pleiotropic effects of statins, their use has expanded to the treatment of many other conditions, including ventricular arrhythmias, idiopathic dilated cardio-myopathy, cancer, osteoporosis, and diabetes. Therefore, basic principles of statins´ rhabdomyolysis prevention and treatment consist of the following measures:

- Statin withdrawal or not starting statin therapy in patients with more than one risk factor (e.g. elderly people with poor renal and liver functions).
- If the patient has symptoms of myopathy and CK is 10×ULN (the upper limit of normal – 60 and 400 IU/L) or higher.
- If unpleasant urine odor – like chicken liver, with dark brown discoloration (see Figure 1 – our own experience).

  Statin therapy then should be discontinued.

MATERIAL AND METHODS

The goal of the clinical trial was to determine the incidence of undesirable side effects characteristic for statin provoked myositic myopathy, rhabdomyolysis, nephropathy and hepatopathy to ascertain the occurrence of genetic polymorphisms since now known genes taking part in statins´ metabolism.

The observed group of 198 patients was treated with statins, primarially fluvastatin and rosuvastatin. In only 15 of the total group atorvastatin was administered. In this total group there were 126 patients´ subgroup (mean age = 58.3±4.1; male 91, mean age = 57.4±5.9; female 35, mean age = 60.5±6.5), metabolized out of the liver where we administered rosuvastatin. There was, in the subgroup, only pure primary hypercholesterolemia.

RESULTS

The mean value of blood cholesterol before the treatment was 7.8±1.6 mmol/l. During the course of treatment, the mean value of blood cholesterol decreased to 4.83±0.91 mmol/l ($p<0.01$ level of significance). Undesirable muscular signs and symptoms (muscle tenderness, painful muscular spasms, muscle wasting, painful tendons) were present in 32 (25.39%) patients. Muscle symptoms and signs were not in correlation with the level of CK and AST. Among the 32 patients with such disorders in 11 (8.73% of the total 126) CK level increases maximally to 4 times ULN, in 6 (4.7%) statins were excluded because of very intense subjective suffering. CK levels in the frame of 2–5 times ULN were present in 9 (7.14%). CK blood levels over 10 times ULN or higher according to international recommendation indicate in 2 (1.58%) statins´ exclusion. Increased levels of the further muscular mitochon-drial enzyme AST by 5 times ULN were observed in 16 (12.69%), up to 10 times ULN in 2 (1.58%), and over the 10 times ULN also in 2 (1.58%). Both enzyme level distributions were significantly changed during rosuvastatin administration.

We observed rhabdomyolysis in 6 patients (3.03% of the total 198 patients group) using other types of the statins (three of them undergo chronic hemodialysis). In this small group we have performed molecular-genetic analysis of the following proteins relating to statin myopathy: SLCO1B1(388AA/AG-521TT) – (discovered polymorphism in 1 patient), further cytochroms Cyp 2C9 (in 1 patient), 2C8 (in 1 patient), Cyp SA/4 (non discovered positivity) and finally UGT1A1*2B (discovered in 2 patients).

In the group of patients treated by rosuvastatin, we discovered not one case with rhabdomyolysis. In each patient with clinically positive rhabdomyolysis (brown urine discoloration, mal-odorous urine, painful muscle cramps, muscle weakness, fatigue) there was present at least one polymorphism of "statins´ genes". Increased activities of CK, CKMB, and AST over reference values were present in more than 1/3 of patients without correlation to clinic symptoms and signs. Even the occurrence of rhabdomyolysis does not correlate with CK level. The necessity to exclude statins was 3 times higher than is stated in the literary data (clinic and pharmaceutical business).

DISCUSSION

Statin myotoxicity ranges from asymptomatic creatine kinase elevations or myalgias to muscle necrosis and, sometimes, rhabdomyolysis – 6 (3.03%) patients in our series but without the lethal end but with renal insufficiency in 3 cases. Statins may also cause an autoimmune myopathy requiring immune suppression treatment – 2 of 32 (6.45%) patients with muscle symptoms and signs in our series. Symptoms of statin induced myopathy include fatigue, muscle pain, muscle tenderness, muscle weakness, nocturnal cramping, and tendon pain (Campbell 2006). Muscle symptoms and signs were also not homogeneous relating to an intensity of subjective-private painful-stress surviving (private experience) therefore they were not in correlation with the level of CK and AST. The following are circumstances for serious undesirable side effect rhabdomyolysis as self-standing or adding etiologic factors: Advanced age, renal and hepatic failure, hypertriglyceridemia, thyroid dysfunction, exercise, marathon running, Asian race and perioperative period are accepted risk factors (Antons 2006). Despite the fact of CLAM has been described as a necrotizing myopathy (Nakahara *et al.* 1998), some authors have noted a relative absence of muscle fiber degeneration, even in patients with marked weakness and elevated CPK (Creatine phospho-kinase). The relative absence of abnormal spontaneous activity and myopathic MUP (motor unit potential) in patients with severe weakness and extremely high CPK levels was previously noted in rhabdomyolysis and constitute a dissociation between clinical and electrophysiological findings (AlSheKhlee *et al.* 2005). The pathophysiological explanations for such dissociation are unknown. They suggest that statins can modify the excitation-contraction coupling due to increased intracytoplasmatic calcium concentration as a result of dysfunction of the sarcoplasmic reticulum.

The electromyographic findings with myopathic recruitment samples are in agreement with muscle membrane leakage and absence of severe muscle necrosis in the pathologic studies (Victor & Sieb 1994). These electrophysiological findings are helpful to differentiate rhabdomyolysis from fulminant inflammatory myopathies, avoiding muscle biopsy in the former (AlSheKhlee *et al.* 2005). Myotonic potentials have

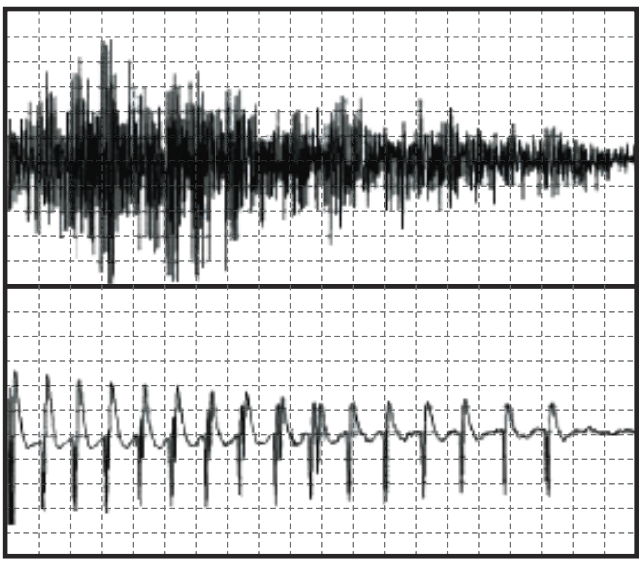

Fig. 2. EMG-Myotonic potentials in the right deltoid muscle. (Diogo Fraxino de Almeida, 2008)

been described in experimental statin-induced myopathy, but only one isolated report out of five patients has shown such potentials in humans (Meriggioli 2001). These were described and registered by Diogo Fraxino *et al.* (2008) (Figure 2). A decreased chloride channels conductance was thought the mechanism in rabbits. This conductance is regulated by the calcium-phospholipid-dependent protein kinase, a known lipid-regulated protein (Johnson *et al.* 1998). The dysfunction of the sarcoplasmic reticulum membrane may activate the protein kinase and decrease of chloride conductance, resulting in myotonia (De Luca *et al.* 1994). In animal models, myotonic potentials are the cardinal feature (Nakahara *et al.* 1992; Nakahara *et al.* 1998). However, the rarity of myotonic potentials in humans when compared with animal models suggests a different pathophysiologic mechanism (Sonoda *et al.* 1994). Tavee & Panettiere (2004) reported a family with myotonia unmasked by simvastatin prescribed for familial hyperlipidemia. Electrophysiological and genetic testing were consistent with autosomal dominant myotonia congenita. The clinical and electrophysiological myotonia persisted even after discontinuation of the statin. The authors believe that the medication by statin may have been a triggering factor of the chloride channel dysfunction in a genetically susceptible patient for clinical and electrical myotonia. The complete recovery clinical and electrophysiological abnormalities after the statin discontinuation suggests a direct effect of the drug in pathophysiology of the muscle disorder in all our patients. Although inflammatory myopathy can be accompanied by myotonic potentials in the needle EMG, the absence of profuse abnormal insertional activity as well as the rarity of myopathic motor unit potentials, and the spontaneous improvement of the clinical, laboratory and electrophysiological abnormalities after discontinuation of the statin make this diagnosis unlikely. Some drugs such as the glucocorticoids have a predictable dose related effect and will induce myopathic weakness in any individual treated with sufficiently large doses for long enough (Victor & Sieb 1994). There is an idiosyncratic vulnerability the nature of which is sometimes poorly understood. But there are the polymorphisms (Carr *et al.* 2013) of "statins´genes" present in all our 6 patients with rhabdomyolysis previously considered as idiosyncratic. While the potential for glucocorticoids, statins, and a number of other therapeutic agents to cause myopathy is well established, in the case of some of the other drugs that have been implicated in case reports the evidence is more tenuous and an etiological link remains unproven. Nerve conduction studies are usually normal and needle EMG is useful to detect myopathic changes in some, but not in all patients. The relative absence of abnormal spontaneous activity and myopathic MUP's in patients with severe weakness and extremely high CK levels was previously noted in rhabdomyolysis and constitute a dissociation between clinical and electrophysiological findings (AlSheKhlee *et al.* 2005). These electromyographic findings are in agreement with muscle membrane leakage and the absence of severe muscle necrosis in the pathologic studies (Victor & Sieb 1994).

By means of such electrophysiological findings, it is possible to differentiate rhabdomyolysis from fulminant inflammatory myopathies, avoiding muscle biopsy in the former (AlSheKhlee *et al.* 2005). Statin intake may be a sufficient insult to precipitate neuromuscular symptoms and substantially increase levels of muscle enzymes in pre-symptomatic patients with silent abnormal neuromuscular substrate, e.g. metabolic myopathy with myophosphorylase deficiency and with acid maltase deficiency (Tsivgoulis *et al* 2006). Statins´ rhabdomyolysis is not an auto-aggressive inflammation. It is cholesterol lowering agents necrotizing myopathy (CLAM). Although inflammatory myopathy can be accompanied by myotonic potentials in the needle EMG, the absence of profuse abnormal insertional activity as well as the rarity of myopathic motor unit potentials, and the spontaneous improvement of the clinical, laboratory and electrophysiological abnormalities after discontinuation of the statins make this diagnosis likely.

The following authors believe that the medication may have been a triggering factor of the chloride channel dysfunction in a genetically susceptible patient for clinical and electrical myotonia (Tavee & Panettiere 2004). Our private remarks consist of the following questions:

- How many persons, under statins´ treatment, suffer from chronic fatigue syndrome?
- How many fatigue persons before statins´ treatment suffer from rhabdomyolysis during course of the cure?
- How many persons with silent predispositions for metabolic myopathies are unmasked by statins?

We would like to perform retrospective epidemiologic study for possible discovering and answering these questions. We should say together with Sir Winston Churchill:

"Now this is not the end (of the knowledge about the statins´ unpleasant effects). It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

The essential principle for each treatment procedure "*nihil nocere*" also is valid for statins´ treatment. It means, a comparison of the statins with placebo says respectively about both similar tablet's pathogenetic action provoking gene expression and pathologic change of the skeletal muscle respiratory chain, muscle degeneration, and possible inflammation. It doesn't mean an advantage for statins, but also the same risk with the placebo. Stopping of statins´ treatment in our

patients leads to complete recovery of muscle affection. It is possible to attenuate the negative influence of statins by means of subcutaneous evolocumab in diverse populations, including statin-intolerant patients (Cho *et al.* 2013).

CONCLUSION

Among muscle cramps as side effects of statin therapy, there are mainly spasms as a result of myositic myopathy, but sometimes also unmasked myotonic contractions are visible. Such, relatively light undesirable muscular signs and symptoms (muscle tenderness, painful muscular spasms, muscle wasting, painful tendons) were present in 32 (25.39%) patients. Among the 32 patients with the mild disorders an auto-immune myopathy requiring immune suppression treatment in 2 of 32 (6.45%) in 11 (8.73% of the total 126) CK level increases maximally to 4 times ULN and in 6 (4.7% of the total 126) statins were excluded because of very intense subjective suffering. CK levels in the frame of 2–5 times ULN were present in 9 (7.14%). CK levels over 10 times ULN or higher according to international recommendation indicate in 2 (1.58%) statins´ exclusion. Increased levels of the further muscular mitochondrial enzyme AST by 5 times ULN were observed in 16 (12.69%), up to 10 times ULN in 2 (1.58%), and over the 10 times ULN also in 2 (1.58%). We observed 6 (4.68%) patients with rhabdomyolysis during CLAM treatment who should be included in the differential diagnosis. After the first symptoms and signs there are also later myoglobinuria with odor – like chicken liver, visually dark color of urine, fatigue syndrome, reversibility of all at early statin withdrawal. The statin myopathy is visible in EMG as the absence of abnormal spontaneous activity and myopathic MUP's in patients with severe muscle weakness and extremely high CK levels, which differentiate rhabdomyolysis and auto-aggressive myositic myopathy. We observed rhabdomyolysis in 6 patients (3.03% of the total 198 patients group) using other types of the statins. In this small group we have performed molecular-genetic analysis of the following proteins relating to statin myopathy: SLCO1B1(388AA/AG-521TT) – (discovered polymorphism in 1 patient), further cytochroms Cyp 2C9 (in 1 patient), 2C8 (in 1 patient), Cyp SA/4 (non discovered positivity) and finally UGT1A1*2B (discovered in 2 patients). In the group of patients treated by rosuvastatin we discovered not one case with rhabdomyolysis. In each patient with clinically positive rhabdomyolysis (brown urine discoloration, mal-odorous urine, painful muscle cramps, muscle weakness, fatigue) was present at least one polymorphism of "statins´ genes". Increased activities of CK, CKMB, and AST over reference values were present in more than 1/3 of patients without correlation to clinic symptoms and signs. Even the occurrence of rhabdomyolysis does not correlate with a CK level. Necessity to exclude statins was 3 times higher than is stated in the literary data (clinic and pharmaceutic business).

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