Severe Rhabdomyolysis after Uneventful Long Term Low Dose Statin Therapy

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Abstract

Rhabdomyolysis is a widely recognized yet rare complication in Statin use. Rhabdomyolysis might be triggered by prescription of high doses of Statins or by Statin accumulation due to interactions with concomitant medication. Muscle cell destruction as evidenced by myoglobin elevation can induce potentially life threatening acute renal failure known as crush kidney. Here, we report a case of a sudden severe rhabdomyolysis with consecutive renal failure in a patient who received low dose Statin-therapy for 6 years without previous complications.

Keywords: Rhabdomyolysis; Statin therapy; Statin-associated myopathies (SAM)

Introduction

Statins are a common group of cholesterol lowering pharmaceuticals, with the shared pharmacodynamical characteristic of 3-HMG-CoA inhibition, the key enzyme in cholesterol synthesis [1,2]. Inhibition of 3-HMG CoA by Statins is the most effective way of lowering low density lipoprotein cholesterol (LDL). LDL levels correlate directly with cardiovascular mortality. Numerous randomized controlled trials confirmed and stressed the Statin-mediated therapeutic benefit [3-5]. Statin significantly reduces the risk for cardiovascular death, myocardial infarction, for stroke and the risk for arterial revascularization therapy [3-5]. Statin therapy aiming at lowering the cardiovascular risk is an established and well tolerated way of reducing the cardiovascular risk. These benefits are clear for high doses of Statins or by Statin accumulation due to interactions with concomitant medication. Muscle cell destruction as evidenced by myoglobin elevation can induce potentially life threatening acute renal failure known as crush kidney. Here, we report a case of a sudden severe rhabdomyolysis with consecutive renal failure in a patient who received low dose Statin-therapy for 6 years without previous complications.

Case History

levels had normalized (Figure 2).

**Table 1:** Patient lab data at time of hospitalization.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>&gt; 334 µkat/l</td>
<td>0.63 – 2.91 µkat/l</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>21896 µg/l</td>
<td>28-72 µg/l</td>
</tr>
<tr>
<td>ASAT</td>
<td>4.54 µkat/l</td>
<td>0.17-0.85 µkat/l</td>
</tr>
<tr>
<td>LDH</td>
<td>22.54 µkat/l</td>
<td>2.25 – 3.75 µkat/l</td>
</tr>
<tr>
<td>Creatinin</td>
<td>596 µmol/l</td>
<td>59-104 µmol/l</td>
</tr>
<tr>
<td>GFR MDRD</td>
<td>8.7 ml/min</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>50.7 mmol/l</td>
<td>&lt;11.9 mmol/l</td>
</tr>
<tr>
<td>TSH</td>
<td>0.928 µU/l</td>
<td>0.4-3.77 µU/l</td>
</tr>
</tbody>
</table>

*CK: Creatinkinase; ASAT: Aspartat-Aminotransferase; LDH: Lactatdehydrogenase, GFR: Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease; TSH: Thyreotropin.

**Figure 1:** A: Skeletal muscle with numerous, scattered necrotic fibres (*) without signs of inflammation (H&E × 100), B: Single skeletal muscle fibre in the state of myophagocytosis (H&E × 200); (†) marks another fresh single fibre necrosis, C: Detection of c5b9-positive immunocomplexes on small vessels (arrowheads), endomyosial capillaries and sarkolemmal and cytoplasmativ in necrotic muscle fibres (c5b9 × 200), D: Clear sarcolemmal and cytoplasmatic upregulation of MHC class I (MHC-I × 100).

**Figure 2:** Timely normalization of myoglobin- and CK- levels after initiating supportive therapy (CVVH) and cessation of Statin medication.

**Discussion**

In clinical practice up to 10% of patients receiving Statin therapy develop at least mild forms of myopathy, an underestimated side effect supported by the Primo Trial [14]. Given the context of more than 3.2 billion prescriptions in Germany in 2012 a large number of affected or symptomatic patients are to be expected. Almost 30% of Statin associated incidences occur within the first year of treatment [15]. However onsets of muscular side effects have been documented between 2 month and up 10 years after initiation of Statin therapy [16]. Thus, a long standing uneventful and well tolerated Statin therapy as in our patient with sudden rhabdomyolysis after 6 years confirms these observations. Statin associated muscle problems vary considerably. Some patients with high CK level do not present with any muscle weakness until they reach a critical value [16]. On the other hand there are patients with distinct muscle parses at a lower mild CK level. Cessation of Statin medication usually leads to a fast recovery of muscle related symptoms.

The exact mechanism of Statin associated myopathies (SAM) still remains elusive. Several theories exist ranging from membrane destabilization due to decreased cholesterol content of skeletal muscle plasma membrane, impaired mitochondrial function due to coenzyme Q10 depletıon, disturbed calcium metabolism and vitamin D deficiency [10]. Also, there are various co-medications that increase the risk of Statin associated myopathy, mostly by interference of the metabolizing cytochrome p 450 system (CYP3A4, CYP2C). Especially the fibrac acid derivative gemfibrozil is known to aggravate symptoms and severity of Statin associated myopathy. The development of Statin associated muscle problems is dose-dependent [8]. Nevertheless severe cases of SAM have been reported in patients under low dose Statin medication and without interfering medication. Documented co-medication in the presented case was devoid of potentially interfering drugs. However, personal communication with the patient’s family doctor revealed an additional Colchicine medication in close temporal vicinity of clinically manifest rhabdomyolysis. Colchicine was prescribed as muscle pain was misinterpreted as a potential goat attack. Colchicine itself can cause myopathy. Concomitant treatment of Colchicine and Simvastatin may exacerbate its myotoxic effect [17].
Before excretion Colchicine is metabolized in the liver by demethylation. Statin metabolism may compete with Colchicine for the CYP3A4-isoenzym leading to higher serum concentrations of both medications, thereby increasing the risk of side effects.

Of note, also genetic predisposition is discussed to cause Statin associated myopathies (SAM). Developing muscle symptoms are more frequent in patients with inborn metabolic muscle diseases such as McArdle disease or MADA-deficiency [8]. In these cases, Statin medication can unmask these underlying genetic muscle diseases [12]. Also mutations or polymorphisms of genes related to regulate serum Statin levels are known to cause a higher risk of developing SAM. Also genes responsible for muscle vascularisation, those affecting intracellular Statin concentration in muscle cells and genes responsible for muscle tissue energy metabolism are associated with SAM [15]. Metabolic disease (McArdle, MADA-deficiency) was excluded in the muscle biopsy of the presented case. Genetic testing was not performed. Advanced age, female sex, low body mass index, alcohol consumption are further predisposing factors for SAM. Given the high number of prescriptions clinicians are in need for reliable risk evaluation methods for the identification of vulnerable patients.

Clinical relevant rhabdomyolysis is a rare in Statin therapy. Mortality is low with 0.15 deaths per 1 million [18]. However, the FDA - Adverse Event Reporting System identified 147,789 case reports with suspected Statin associated myopathy between 2005 and 2011. The highest rate of rhabdomyolysis was observed for simvastatin [19]. Rhabdomyolysis is defined by CK levels at least 10 times normal and reflects acute and massive muscle fiber necroses and accompanied by the release of muscle related metabolites into the bloodstream [16].

Clinical monitoring of Statin associated myopathy may include baseline CK levels of patients especially if there are risk factors as impaired renal function, genetic myopathy in the past medical history or significant alcohol abuse [8,15]. Co-medication should be checked for potential interaction with Statins, especially if new medication is prescribed including herbal cures. Patients with muscle related symptoms and Statin medication should immediately checked for CK increase. Medication should be stopped immediately and CK levels monitored. In case of persistent elevated CK levels after cessation of Statin medication other causes of elevated CK levels should be considered and investigated, including anti HMG-CR associated SAM [15]. Patients should be informed about the risk developing myopathy and symptoms. Despite the risk of SAM Statin therapy remains a use- and powerful tool in cardiovascular risk reduction and in reducing cardiovascular morbidity and mortality. Their benefits considerably supersede their risk profile [9]. Our case emphasizes the need for clinicians to be aware of Statin associated necrotizing myopathy even after long term Statin treatment. The presented patient received uneventful Simvastatin therapy for a period of six years. In addition, we identified Colchicine as potential trigger of SAM in our patient based on its potentially competing metabolism with Statin. Fast recognition of SAM is mandatory to rescue renal function and avoid life threatening complications. The treatment of choice remains immediate cessation of Statin medication and supportive care for renal function. If recognized early enough, outcome is excellent.

Conflicts of Interest
We declare no conflicts of interest.

References