Rheumatol Int (2008) 28:289–291
DOI 10.1007/s00296-007-0435-1

CASE REPORT

Which statin should be used together with colchicine? Clinical experience in three patients with nephrotic syndrome due to AA type amyloidosis

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Received: 6 November 2006 / Accepted: 22 July 2007 / Published online: 17 August 2007

Abstract Colchicine and statins are well known drugs that cause myopathy and neuropathy. Co-administration of certain drugs with statins may increase myotoxic effect, causing myopathy and varying degrees of rhabdomyolysis. Therefore, it is very crucial to know which statin should be used during a combination therapy including colchicine and other drugs. We present three cases with AA amyloidosis secondary to familial Mediterranean fever, who developed neuromyopathy while receiving the combination of colchicine and statin. We also briefly discussed the different metabolic pathways of statins and colchicine when used together.

Keywords Amyloidosis · Colchicine · Familial Mediterranean fever · Neuromyopathy · Statins

Introduction

Some chronic inflammatory diseases such as familial Mediterranean fever (FMF), rheumatoid arthritis and Behcet's disease may result in AA type amyloidosis and nephrotic syndrome [1, 2]. Over time, this process may progress to renal failure. In order to halt this process, a combination of colchicine and statins is used for the treatment of amyloidosis and hyperlipidemia [3, 4]. However, this combination may give rise to neuromyopathy [5]. Since statins have a different metabolic pathway in the liver, there are bound to be differences between statins in terms of myopathic adverse effects, particularly when combined with colchicine. Therefore, great care must be taken while choosing the type of statin to be used alongside colchicine. This report presents three cases suffering from AA amyloidosis secondary to FMF. These patients developed neuromyopathy while on a combination of colchicine and statin. We also briefly discuss metabolic pathways of statins and colchicine when they are used together.

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Report of cases

Case 1

A 43-year-old man with a 4-year history of FMF was admitted to our hospital with edema of both lower extremities. He would neglect to take colchicine on a regular basis despite having been urged to do so. Renal biopsy was performed for his nephrotic range proteinuria, which confirmed AA type renal amyloidosis. Colchicine was started in doses of 1.5 mg/day. Atorvastatin was added to the treatment in doses of 10 mg/day 2 months later. Two weeks after the addition of atorvastatin, the patient developed muscle pain and weakness. Physical examination revealed proximal muscle weakness in the upper and lower extremities (3/5). In both muscle groups, there was moderate decrease on his sense and vibration examinations.

Laboratory data were as follows: erythrocyte sedimentation rate 140 mm/h, serum creatinine 1.4 mg/dl (N: 0.5–1.4), blood urea nitrogen 13 mg/dl (N: 5–20), total protein

4.7 g/dl (N: 4.5–7), albumin 2.4 g/dl (N: 3.5–5), cholesterol 305 mg/dl (N:112–200), creatine kinase 608 U/l (N:16–190), AST 38 U/l (N: 0–40), ALT 24 U/l (0–40). C-reactive protein level was 4.71 mg/dl (N < 0.8). Glomerular filtration rate (GFR) was 71.5 ml/min per 1.73 m^2. Other biochemical and serological tests were within normal limits. Electroneuromyography (ENMG) showed a widespread sensory motor neuropathy along with myopathic pattern.

Both drugs were discontinued. The symptoms disappeared and enzyme levels returned to normal by the beginning of the third week. Colchicine was restarted in low doses, which were later increased at a slow pace with no recurrence of myopathy or an increase in enzyme levels.

Case 2

A 30-year-old male patient had been suffering from AA type renal amyloidosis due to FMF since 10 years, due to which he had been put on regular colchicine (1.5 mg/day). Simvastatin (20 mg/day) was added to the treatment because of hyperlipidemia. After 3 weeks, he was admitted to hospital with muscle pain, weakness and cramps. Physical examination showed proximal muscle weakness in the upper and lower extremities (2–3/5). The power of distal muscles was normal. Sense and vibration examinations showed a mild decrease in both muscle groups.

Laboratory data were as follows: serum creatinine 1.28 mg/dl (N: 0.5–1.4), BUN 13 mg/dl (N: 5–20), cholesterol 263 mg/dl (N: 112–200), creatine kinase 1,232 U/l (N: 16–190), AST 67 U/l (N: 7–39) and ALT 71 U/l (N: 2–40). Proteinuria was 9 g/day. GFR was 76.4 ml/min per 1.73 m^2. ENMG showed a widespread sensory motor neuropathy.

Both of the drugs were discontinued due to suspicion of drug-associated myopathy. By the end of the second week after the discontinuation of the drugs, his myopathic symptoms had already disappeared and his enzyme levels had returned to normal. A new colchicine treatment was started in low doses (0.5 mg/day) and it was gradually pushed up (1.5 mg/day). In the follow-up period, there were no symptoms of myopathy or increase in enzyme levels.

Case 3

A 41-year-old male patient had had AA type renal amyloidosis due to FMF since 15 years and he regularly took 1 mg/day colchicine. During his routine control, hyperlipidemia was observed and atorvastatin 20 mg/day was launched. The patient was admitted to hospital with dyspnea and muscle pain 20 days after the onset of the atorvastatin treatment. Physical examination revealed proximal muscle weakness of the upper and lower extremities (2/5). The strength in the distal limb musculature was normal. There was a mild decrease of sense and vibration in both muscle groups.

Laboratory data were as follows: serum creatinine 1.39 mg/dl (N: 0.5–1.4), BUN 27 mg/dl (N: 5–20), cholesterol 283 mg/dl (N: 112–200), creatine kinase 11,069 U/l (N: 16–190), AST 342 U/l (N: 7–39) and ALT 347 U/l. Proteinuria was 4 g/day. GFR was 74.5 ml/min per 1.73 m^2. ENMG showed a widespread sensory motor neuropathy associated with myopathy.

Once the drugs had been discontinued, it was observed that his myopathic symptoms disappeared within one week and enzyme levels returned to normal two weeks later. A new colchicine treatment was started in low doses, which were gradually pushed up to 1.5 mg/day. The follow-up examination showed normal clinical and biochemical data.

Discussion

Statins are metabolized by the cytochrome P450 system. CYP3A4 is one of the major isoenzymes of the cytochrome P450 group. This isoenzyme metabolizes some HMG-Co A reductase inhibitors, such as lovastatin, simvastatin, and atorvastatin. Fluvastatin is metabolized by CYP2C9 and pravastatin has minimal metabolism by CYP3A4 and is primarily cleared by the kidneys. Cerivastatin is metabolized by both the CYP3A4 and CYP2 C8 systems [6, 7]. When statins are used simultaneously with an agent that is metabolized by the cytochrome P450 system, there is accumulation of both substrates, which increases the potential for adverse drug reactions. This is the mechanism by which concurrent use of some drugs with statins induces adverse reactions [8–10].

Colchicine is excreted by the hepatic-biliary system. Demethylation in the liver before excretion depends on the availability of an isoenzyme of CYP450, CYP3A4 [5, 11]. Simvastatin and atorvastatin compete with colchicine for CYP3A4, resulting in impaired hepatic demethylation of the latter when applied together. Renal insufficiency further exacerbates the problem of impaired excretion. The concentration of colchicine or statin might have built up rather quickly and induced myopathy [11].

Our patients presented with muscle weakness, CK elevation, and neuromyopathy after starting the statins (atorvastatin in two patients and simvastatin in one) while still receiving colchicine. Considering the fact that the patients were not exposed to any other drugs or diseases to impair their renal and liver functions, we assumed that addition of the statins into the colchicine treatment could act as the main factor for the development of neuromyopathy. Resolution of the symptoms of the patients, as well as normalization of their CK enzymes following the discontinuation of colchicine and statins, led us to suspect that combining

statins with colchicine could account for neuromyopathy. Because re-administration of colchicine without statins did not result in any CK elevation or muscle weakness in these patients, we believe that statins could play a role in altering metabolism of colchicine, which might in turn result in toxicity.

The present study concluded that physicians should be alert to a possible interaction between colchicine and statins. If a combination of statin with colchicine is to be considered, care should be taken to use such statin drugs as fluvastatin and pravastatin that tend to be metabolized outside the CYP3A4 system.

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