Rare disease

Use of once-weekly statin in combination with ezetimibe in a patient with mitochondrial disease

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Summary

The authors describe a patient with personal and family history of muscle pains highly suggestive of mitochondrial disease. She presented with familial combined hyperlipidaemia with family history of premature coronary artery disease. After 4-week therapy of 5 mg of rosuvastatin once a week combined with 10 mg of ezetimibe daily, the low-density lipoprotein cholesterol level was markedly decreased from 3.88 to 2.82 mmol/l (27.3% reduction). She has experienced no adverse effects after 6 month treatment. The results suggest that the combination therapy of low-dose once-weekly rosuvastatin and daily ezetimibe could be used as an effective regimen for patients with mitochondrial disease.

BACKGROUND

Mitochondrial diseases are a heterogeneous group of disorders that can affect multiple organs with varying severity.¹ It can be a primary disorder caused either by a genetic defect in the mitochondrial DNA or the nuclear DNA, or a secondary disorder resulting from mitochondrial toxins (eg, high activity antiretroviral therapy), certain primary neurodegenerative disorders (eg, Alzheimer's disease and Parkinson's disease).² Mitochondrial disease is also associated with ageing. Statin mediated mitochondrial dysfunction has also been reported.³

Primary mitochondrial diseases affect up to 1 in 5000 people.⁴ They manifest with variety of symptoms including cardiomyopathy, stroke and stroke-like episodes, visual symptoms, eye movement abnormalities, sensorineural hearing loss, diabetes, disorders affecting the central and peripheral nervous system, as well as myopathy. Exertional myalgia is a common presentation of mitochondrial disease, especially in adults. As one of the side effects of statins is myopathy, use of statin therapy may exacerbate the symptoms of myalgia in patients with mitochondrial disease. Patients with mitochondrial disease are considered to be vulnerable to statins.⁵ Some reports suggest that the use of statins is associated with myotoxicity⁶ and exacerbation of symptoms related to mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS).⁷ Here we describe a patient with personal and family history highly suggestive of mitochondrial disease also diagnosed with familial combined hyperlipidaemia who tolerated low-dose of rosuvastatin therapy once a week with a marked improvement in her lipid profile.

CASE PRESENTATION

A 57-year-old woman was referred to the lipid clinic for the management of familial combined hyperlipidaemia. She had positive family history of premature coronary artery disease. Her medical history included hearing loss, muscle weakness and exercise intolerance. Muscle biopsy performed in 2003 showed a significantly decreased

activity of complex IV of the electron transport chain. Thus she met the Bernier criteria⁸ for probable mitochondrial disease. The common MELAS and myoclonic epilepsy with ragged red fibres mutations were not present in the muscle tissue. She has never been on any lipid-lowering medications.

Her lipid profile revealed low-density lipoprotein cholesterol (LDL-C) of 3.88 mmol/l and triglycerides of 1.64 mmol/l (table 1). The liver, thyroid and kidney function tests were all normal. Echocardiogram showed no abnormalities. Carotid ultrasound showed that there was several mild focal plaques in their internal carotid arteries.

Due to her high cardiovascular risk (greater than 30% on the Framingham risk score) and positive family history of premature coronary artery disease (her mother had a silent myocardial infarction at the age of 46), we started low-dose rosuvastatin 5 mg once a week. After 4 weeks of treatment there was only a mild reduction of LDL-C by 12.3% (from 3.88 to 3.40 mmol/l) (table 1). Addition of ezetimibe at 10 mg once daily was indicated at this point because as she did not reach the LDL-C target. Four weeks after using both drugs, there was a marked reduction of LDL-C (27.3%) (table 1). There were no changes in her dietary habits during the treatment period. The patient tolerated the low-dose rosuvastatin well without any worsening of her muscle symptoms after close follow-up for 6 months so far. Most importantly, the combined treatment with statin and ezetimibe resulted in the patients' lipids approaching the target recommended by Canadian 2009 guidelines.⁹

DISCUSSION

Muscle pain is the most common adverse effects of statin therapy.^{10 11} It occurs in upto 10% of patients. Recognised risk factors for statin associated myopathy include diabetes, chronic kidney disease, family history, vitamin D deficiency and inborn error of metabolism.^{7 12} In this report, we describe a patient with probable mitochondrial disease who responded well to 4-week combination therapy

Table 1 Biochemical results after 4-week combination therapy of rosuvastatin and ezetimibe

	TC (mmol/l)	LDL-C (mmol/l)	HDL-C (mmol/l)	TG (mmol/l)	Apo B (g/l)	CK (IU)	Fasting glucose (mmol/l)	HbA1C (%)	ALT	AST
Before the treatment	5.37	3.19	1.11	2.36	1.08	196	6.1	6.1	24	26
After the treatment with weekly statin and ezetimibe	4.13	2.13	1.07	2.05	0.85	213	5.8		30	
Before the treatment	5.79	3.88	1.16	1.64	–	246	6.0	6.3	22	20
After the treatment with weekly statin only	5.09	3.40	1.03	1.46	–	246			22	20
After the treatment with weekly statin and ezetimibe	4.70	2.82	1.08	1.75	–	178			29	21

apo B, apolipoprotein B; ALT, alanine transaminase; AST, aspartate aminotransferase; CK, creatine kinase; HbA1C, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol.

of 5 mg of rosuvastatin once a week combined with 10 mg of ezetimibe daily without developing any muscle symptoms. On this regimen, the LDL-C was significantly decreased from 3.88 to 2.82 mmol/l (27.3% reduction). Interestingly, the patient's younger sister has been diagnosed with possible mitochondrial disease (she had very similar symptoms of hearing loss, muscle weakness and exercise intolerance) who also has familial combined hyperlipidaemia. On the same combination regimen with low-dose rosuvastatin and ezetimibe, there were significant reductions of 33.2% (from 3.19 to 2.13 mmol/l) in her LDL-C and of 21.3% (from 1.08 to 0.85 g/l) in apoB (table 1). She has also not experienced any muscle problems after 4-month follow-up. In both cases, the lipid profile was done on Monday while the 5 mg of rosuvastatin was taken on Wednesday. It has recently been reported that 5–20 mg once-weekly rosuvastatin is effective in lowering LDL-C (12.2% to 29% reduction) in patients with history of statin intolerance.^{13 14} In our case, the addition of ezetimibe to 5 mg once-weekly statin regimen further reduced LDL-C levels by 27% without producing any side effects.

CONCLUSION

We report a patient with probable mitochondrial disease who responded well to 5 mg once-weekly rosuvastatin combined with 10 mg ezetimibe daily. The combination therapy was well tolerated with no muscle symptoms after close 6 month follow-up.

Learning points

- ▶ Mitochondrial disease is a risk factor for statin intolerance.
- ▶ Addition of 5 mg of rosuvastatin once a week to daily ezetimibe significantly decreases LDL-C.
- ▶ This regimen is well tolerated in an individual with mitochondrial disease (who is in risk for statin intolerance).

Competing interests None.

Patient consent Obtained.

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