CASE REPORT

A generalised sensation of coldness following introduction of rosuvastatin therapy

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SUMMARY

Rosuvastatin is the most potent 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor commercially available to lower low-density lipoprotein cholesterol. Rosuvastatin has been associated with several adverse effects, including rhabdomyolysis and arthralgias. Here, we report an unusual adverse effect occurring on treatment with rosuvastatin, a 'continuous sensation of coldness'. A 60-year-old man began experiencing this peculiar feeling shortly after introduction of rosuvastatin treatment. The gentleman had to wear extra pair of socks and cover himself with blankets while reading, even during summer with surrounding temperature above 30°C. The abnormal sensation persisted for the 26 months during which he was treated with rosuvastatin, and disappeared within a week after discontinuing treatment. Physical examination, including thorough neurological examination, was entirely normal, as were haematological and biochemical parameters. While the pathophysiology of this phenomenon remains unknown, we hope that this case will encourage others to report similar symptomatology, perhaps enabling to gain more insight on the condition.

BACKGROUND

Rosuvastatin is a commonly-prescribed lipid-lowering drug. Although several adverse effects occurring under rosuvastatin therapy have been described, we report here a new side effect of rosuvastatin.

CASE PRESENTATION

A 60-year-old man with elevated low-density lipoprotein (LDL) cholesterol was prescribed rosuvastatin (Crestor) 5 mg daily to treat dyslipidaemia. Medical history was significant for benign prostate hypertrophy, treated with dutasteride (Avodart, 0.5 mg daily) and tamsulosin (Flomax, 0.4 mg daily), as well as arterial hypertension, treated with valsartan (Diovan, 80 mg daily). The man had previously been treated with fenofibrate (Lipidil Supra, 160 mg daily) for hypertriglyceridaemia and the medication was well tolerated. Fenofibrate was withdrawn before rosuvastatin was introduced, as it was deemed more important to lower the LDL cholesterol (3.49 mmol/L), despite triglycerides levels remaining elevated (1.95 mmol/L, with target therapeutic values <1.70 mmol/L).

A few months after the introduction of rosuvastatin therapy, he began experiencing an almost continuous 'sensation of coldness originating from within'. This unusual sensation developed progressively, and eventually reached a point where, even

during summer, the patient would have to wear a double pair of wool socks and would sometimes have to cover himself with a blanket while watching TV or reading a book, despite an ambient temperature above 30°C. At night, he would sleep with wool socks and several bed sheets despite an ambient temperature above 25°C. He described this sensation as a being an 'inner sense of coldness that would not respond to increase in ambient temperature, or putting on more clothes, and would affect his whole body, not being limited to the extremities'. This abnormal sensation significantly impaired his quality of life and eventually affected his mood.

Vital signs remained normal. Body temperature was normal, without fever or hypothermia. Physical examination was normal; there was no sign of cardiac, arterial or venous insufficiency. Skin temperature was normal throughout, and was sometimes warm, certainly not cold. There was no skin discoloration. Neurological testing was normal; specifically, there was no evidence of peripheral neuropathy with vibration being well perceived distally, proprioception normal. Thermoalgaesic sensory modalities were also normal. Thyroid function test was normal (1.41, normal range 0.35–5.00).

This sensation of coldness emanating from within was accompanied by adverse effects more commonly encountered on rosuvastatin intake, such as diffuse pain and arthralgias, at times preventing him from playing the piano. Haematological and biochemical parameters, including creatine kinase and liver function tests always remained normal.

OUTCOME AND FOLLOW-UP

The patient remained on rosuvastatin 5 mg daily for 26 months, after which the therapy was discontinued. Within a week of rosuvastatin discontinuation, the inner sensation of coolness disappeared and he could stop wearing extra pairs of socks and covering himself with blankets. Since his LDL cholesterol rose above 3.50 mmol/L a few weeks after discontinuation of rosuvastatin, he was put on simvastatin (Zocor, 10 mg daily). He has now been taking simvastatin for 4 months and the sensation of coldness emanating from within has not resumed.

DISCUSSION

Rosuvastatin is the most potent commercially-available 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor used to lower LDL cholesterol.¹ Rosuvastatin is generally well tolerated by patients. However, several adverse effects have been associated with its use. The POLARIS

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study was a clinical trial comparing the lipid-lowering efficacy of rosuvastatin (40 mg daily) and atorvastatin (80 mg daily) in 871 patients. In that study, the most commonly reported adverse events included myalgia, arthralgias, nasopharyngitis, fatigue, back pain, etc.² Similar adverse effects were reported in other clinical trials and integrated database surveillance programme encompassing close to 17 000 patients.^{3 4} Adverse effects associated with rosuvastatin intake usually occur with higher dosage of the drug and, for instance, people taking between 40 and 80 mg of rosuvastatin daily have approximately 1% chance of developing rhabdomyolysis.^{5 6}

Other adverse effects have been reported in the context of case-report studies, such as pemphigoid,⁷ erythema multiforme,⁸ erythromelalgia,⁹ recurrent pancreatitis,^{10 11} thrombocytopenia,¹² gynaecomastia,¹³ as well as short-term memory loss.¹⁴ These unusual adverse effects are currently anecdotal and occurred with doses of rosuvastatin between 5 and 40 mg daily.

To the best of our knowledge, this case report is the first one to describe such a peculiar symptomatology. The patient clearly described his symptoms as feeling cold throughout his body and had a completely normal physical examination, without evidence of factors that could account for his symptoms such arterial insufficiency and peripheral hypoperfusion. Moreover, he did not have any signs/symptoms suggestive of peripheral neuropathy that could have explained this abnormal sensation. Importantly, the condition reported here appears to be benign, as it was not accompanied by alterations of haematological or biochemical parameters.

At the moment, we do not have any hypothesis as to why the patient experienced this altered sensation. However, this case suggests that individuals on rosuvastatin describing similar symptoms might be improved following discontinuation, or perhaps

only reduction, of the HMG-CoA inhibitor. In the case presented here, the gentleman remained on rosuvastatin for 26 months because no one suspected that it was the underlying aetiology of his symptoms; had it been suspected before, it could have been discontinued earlier, which would have considerably improved the patient's quality of life.

The fact that simvastatin has been so far well tolerated raises the following question: might this rare adverse effect occur with any statin or is it inherent to rosuvastatin usage? It is our hope that publication of this case-report study will encourage physicians whose patients have experienced similar manifestations while treated with rosuvastatin or another HMG-CoA inhibitor to disseminate such cases, to gain more insight on the phenomenon described here.

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Competing interests None.

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Learning points

- ▶ A 62-year-old man progressively started experiencing an inner sensation of coldness after being started on rosuvastatin 5 mg daily.
- ▶ This abnormal sensation disappeared after rosuvastatin was discontinued and replaced by simvastatin 10 mg daily.
- ▶ This abnormal sensation appears to be benign, as it is not associated with alterations in haematological and biochemical parameters.
- ▶ Early recognition of this rare complication of rosuvastatin treatment is important, as it appears to be entirely and rapidly reversible after ceasing rosuvastatin treatment.

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