CLINICAL VIGNETTE

Adverse Oral Effects of Statins

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Case

A 61-year-old woman presented with uncontrolled dyslipidemia (LDL 196, non-HDL cholesterol 216, triglycerides 99, HDL 46). She was prescribed treatment with atorvastatin 20 mg daily but stopped it after two weeks because of mouth ulcers that she attributed to the medication. However, she reported that she had also been eating sunflower seeds and that the ulcers may have been caused by abrasion from the hulls. She agreed to re-try atorvastatin but at a lower dose of 10 mg daily. Two weeks later she reported recurrence of mouth sores and the atorvastatin was discontinued. Given the degree of her dyslipidemia she was advised to try an alternate statin and was given a prescription for rosuvastatin 10 mg daily. After 2 weeks she again reported mouth ulcers. The medication was stopped and she was encouraged to pursue non-statin treatments.

Discussion

Statins are one of the most well-established measures to prevent and treat atherosclerotic heart disease. Data from the JUPITER Trial suggested a 54% risk reduction in heart attack and a 48% risk reduction in stroke among people at risk for heart disease who used statins as preventive medicine.[1] Accordingly, statins are among the most widely prescribed medications. More than 200 million people worldwide take a statin, including more than 35 million in the United States, and guidelines suggest that more than 56 million US adults would benefit from being on one.[2]

Mechanism of Action

Statins are competitive inhibitors of hydroxymethylglutaryl (HMG) CoA reductase, the rate-limiting step in cholesterol biosynthesis. They reduce low density lipoprotein (LDL) by 30-63% and triglycerides by 20-40%. They have a modest effect on increasing high-density lipoprotein (HDL) (~5%). They also have anti-inflammatory and other plaque stabilization effects.[2] Statins currently available in the US, in order of increasing intensity, include fluvastatin, pravastatin, lovastatin, simvastatin, pitavastatin, atorvastatin, and rosuvastatin.

Adverse Effects

Like all medications, statins have the potential for adverse effects related to their potency. Atorvastatin, one of the most potent, is associated with more adverse effects than is fluvastatin, which is the least potent. Simvastatin, pravastatin, and lovastatin have intermediate potential for adverse effects.[3] Risk of adverse effect is amplified by drug interactions that functionally increase statin potency, often through inhibition of the cytochrome P450 (CYP)3A4 system. Adverse effects are also increased by factors that affect mitochondrial or metabolic vulnerability, such as metabolic syndrome factors, thyroid disease, and genetic mutations linked to mitochondrial dysfunction.[4]

Rhabdomyolysis is the most severe adverse effect of statin treatment, but also the least frequent, primarily occurring when the drug is co-administered with gemfibrozil or cyclosporine. Increases in creatinine phosphokinase up to 10 times normal have been reported.[3,4] Less severe adverse effects, such as myalgia and increased levels of hepatocellular enzymes and alkaline phosphatase account for about two thirds of adverse effects.[4] Other adverse effects include gastrointestinal (heartburn, nausea, abdominal pain, constipation, diarrhea, flatulence); central nervous system (dizziness, headache, insomnia, paresthesia); and dermatologic (rash, pruritus).[4]

The actual risk of adverse effect, however, appears to be small. Randomized trials have shown only a slight increased risk of adverse reactions to statins compared to placebo, with a total incidence around 5-10%. In addition, some report no increased risk of discontinuing the medication because of adverse effect. In a meta-analysis of 22 placebo-controlled trials of statin use, including nearly 130,000 participants, 13.3 percent of subjects receiving a statin discontinued it compared with 13.9 percent of subjects on placebo (odds ratio 0.99, 95% CI 0.93-1.06) over a mean follow up of 4.1 years.[5]

Many patients who discontinue a statin because of adverse effect may tolerate the same drug or another statin when re-challenged.[6] However, about 25% of patients do not tolerate statin therapy even after changing to a different statin, reducing the dose, or using alternate-day dosing.[7]

Adverse Oral Effects of Statins

There are few reports in the literature of adverse effects of statins in the oral cavity and the pathophysiologic mechanisms for which they occur are not clear.

Smith et al[8] described a 62-year-old man with a 12 month history of recurrent ulcerated keratotic lesions on his tongue.

He was a non-smoker, occasionally drank alcohol, and was taking atorvastatin for hyperlipidemia. Biopsy suggested candidiasis and he was treated with systemic fluconazole and topical nystatin for two weeks. However, the lesions persisted and he presented three months later with two additional oral aphthous-type ulcers. Atorvastatin was then considered as potential cause and discontinued. Symptoms completely resolved over 6 weeks and he had no recurrence.

In a small study by Cruz et al[9] patients aged 50-70 who were being treated with statins were referred to dentistry for oral symptoms including dry mouth and throat (88.5%), cough (46.1%); mucosal itchiness or paresthesia (57.7%;) and bitterness of taste (53.8%). The prescribed statins included simvastatin (n=15), pravastatin (n=7), atorvastatin (n=3), and lovastatin (n=1). The drugs were discontinued for two weeks and symptoms re-assessed. Dryness improved or remitted in 73.9%; cough in 91.7%; bitter taste in 92.8%; and itchiness or paresthesia in 86.7%.

There are few other reports of adverse oral effects of statins. Angioedema is described by Nisly et al[10] in a case of a 75 year old woman with nightly episodes of face, lip, and tongue swelling attributed to simvastatin. Sebok et al[11] report cutaneous lichenoid drug eruptions with oral mucosal involvement in patients taking fluvastatin and lovastatin. Mehregan et al[12] describe two patients who developed cheilitis after beginning treatment with simvastatin. Because epidermal cholesterol synthesis is essential to maintaining the cutaneous barrier function, they postulated that the HMG-CoA reductase inhibitor was causing skin barrier dysfunction in the mucosa.

Given the few reports in the literature, the prevalence of oral manifestations of adverse effects of statins is not fully known, and the pathophysiologic mechanisms for which they occur remain unclear. However, clinicians should be aware of the potential risk and consider statins when a patient on treatment presents with oral complaints.

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