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Case Studies

Marked lowering of high-density lipoprotein cholesterol levels due to high dose bexarotene therapy

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CONTEXT: Bexarotene is a retinoid X receptor agonist, which is currently used for the treatment of cutaneous T-cell lymphoma (CTCL). It is known to induce central hypothyroidism as well as dyslipidemia including elevation of triglycerides (TG) and low-density lipoprotein cholesterol along with slight lowering of high-density lipoprotein cholesterol (HDL-C). Marked lowering of HDL-C has never been previously reported in bexarotene-treated patients and whether it is related to hypothyroidism remains unclear.

CASE REPORT: A 49-year-old African female with a history of CTCL on treatment with bexarotene of 300 mg/d, presented with serum total cholesterol level of 249 mg/dL (6.4 mmol/L), TG level of 92 mg/dL (1.03 mmol/L), HDL-C level of 78 mg/dL (2.02 mmol/L), thyroid stimulating hormone (TSH) of 0.68 μIU/mL, and free thyroxine level of 0.5 ng/dL. Six months later, on increasing the bexarotene dose to 600 mg daily, serum TG increased to 310 mg/dL (3.5 mmol/L) and HDL-C dropped to 3 to 5 mg/dL (0.077–0.13 mmol/L), whereas the TSH was undetectable (0.01 μIU/mL). Despite adequate levothyroxine replacement to 225 μg daily resulting in free thyroxine levels up to 1.5 ng/dL, HDL-C remained extremely low of 4 to 9 mg/dL (0.103–0.233 mmol/L). Bexarotene was discontinued due to poor response of CTCL, 3 months after which her HDL-C levels returned to baseline of 80 to 90 mg/dL (2.07–2.33 mmol/L).

CONCLUSIONS: High dose bexarotene can markedly lower HDL-C levels, which normalize on discontinuation of the drug. Lowering of HDL-C with bexarotene may be due to an increase in cholesterol ester transfer protein activity and appears to be independent of central hypothyroidism.

Introduction

Bexarotene, a vitamin A derivative, is a selective retinoid X receptor agonist, which leads to alterations in cell differentiation, proliferation, and apoptosis. It is approved by the Food and Drug Administration of the United States as a chemotherapeutic agent for refractory cutaneous T cell

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lymphoma (CTCL). Well-known side effects of bexarotene include dose-dependent central hypothyroidism in ~40% of the patients and hypertriglyceridemia in ~60% to 80% of the patients, which is the most important dose-limiting factor.[1–4] Severe hypertriglyceridemia has even resulted in acute pancreatitis in 3 patients.[3] In clinical trials of patients with non-small-cell lung cancer, bexarotene-treated patients with severe hypertriglyceridemia (defined as serum triglycerides (TG) exceeding 5 times the upper limit of normal) had higher rates of hypothyroidism compared with those who remained normotriglyceridemic.[4] This suggests the possibility that hypothyroid state can contribute to dyslipidemia; however, whether dyslipidemia abates after adequate levothyroxine replacement in bexarotene-treated patients remains unclear. Besides hypertriglyceridemia, slight lowering of high-density lipoprotein cholesterol (HDL-C) has also been reported with bexarotene therapy in a few patients.[2] We report extreme lowering of HDL-C with high dose bexarotene therapy, which persisted despite adequate levothyroxine replacement for concomitant hypothyroidism.

Case presentation

This 49-year-old African female developed non-Hodgkin's lymphoma at the age of 37 requiring chemotherapy and stem cell transplantation at the age of 39. Subsequently, she developed relapse of CTCL at the age of 42, which did not respond to donor lymphocyte transfusion, interleukin 2 inhibitor, and other chemotherapeutic agents. She was therefore initiated on bexarotene therapy at the age of 44. At the time of presentation to our facility (month 0), she was taking low dose of bexarotene (300 mg) daily, and she had normal values of serum TG of 92 mg/dL (1.04 mmol/L) and HDL-C of 78 mg/dL (2 mmol/L), but her total cholesterol was 249 mg/dL (6.4 mmol/L), and low-density lipoprotein cholesterol (LDL-C) was 153 mg/dL (3.9 mmol/L), which were elevated (Fig. 1). She denied family history of dyslipidemias or premature coronary artery disease. She did not smoke or consume alcohol. On examination, her body mass index was 24 kg/m^2. She had mild arcus senilis but had no xanthelasmas or xanthomas. She had skin lesions consistent with the CTCL. She was noted to have central hypothyroidism with serum thyroid stimulating hormone (TSH) of 0.68 μIU/mL (normal reference 0.4–4.5 μIU/mL) and free thyroxine level of 0.5 ng/dL (normal reference 0.8–1.8 ng/dL), and levothyroxine replacement was initiated and periodically adjusted (Fig. 1). Thereafter, she was also treated with 20 mg of rosuvastatin daily, which was later switched to 80 mg of atorvastatin due to formulary changes. Due to progression of CTCL, bexarotene dose was increased from 300 to 600 mg daily at month 7 after presentation. Thereafter, marked lowering of HDL-C to 3 to 5 mg/dL (0.077–0.13 mmol/L) along with borderline high TG and extremely low TSH level (0.01 μIU/mL) were noted. At that time, other concomitant oral medications included 10 mg of doxepin daily, 10 mg of lisinopril daily, 12.5 mg of hydrochlorothiazide daily, 5 mg of amlodipine daily, 1000 mg of metformin twice daily, and 40 mg of methoxsalen before phototherapy. Other topical medications include urea 40% cream, tretinoin 0.05% ointment, and triamcinolone 0.1% ointment. Despite increasing levothyroxine dose to 225 μg daily and achieving serum free thyroxine levels of 1 to 1.5 ng/dL, HDL-C stayed extremely low at 4 to 9 mg/dL (0.103–0.233 mmol/L), but serum TG and LDL-C levels showed slight improvement at 19 months after presentation. She was also treated with 80 mg of atorvastatin daily and 6 fish oil capsules daily, which lowered LDL-C and TG levels, but no elevation of HDL-C was noted (Fig. 1). Her bexarotene dose was further increased to 675 mg daily for 8 weeks, but because of poor response of CTCL, the therapy was discontinued. On discontinuation of therapy, serum HDL-C levels normalized within 3 months (Fig. 1). Her central hypothyroidism also started improving, and levothyroxine dose was gradually reduced and finally discontinued with normalization of the thyroid function tests. Naranjo adverse drug reaction probability scale score of +7 suggests that bexarotene was probably related to lowering of HDL-C. This single case report does not constitute a systematic investigation and therefore does not meet the definition of human research according to UT Southwestern Institutional Review Board.

Discussion

Bexarotene-induced hypertriglyceridemia may be partly due to an increase in expression of hepatic lipogenic genes, which increase very low–density lipoprotein (VLDL) production.[5] Furthermore, bexarotene increases apolipoprotein C3, an inhibitor of lipoprotein lipase and thus may reduce catabolic rate of VLDL and chylomicrons.[6] However, the pathophysiology of bexarotene-induced lowering of HDL-C is not well understood. In a study of 10 patients with metastatic differentiated thyroid cancer, 300 mg of bexarotene daily for 6 weeks decreased HDL-C by 30% and apolipoprotein A1 levels by 18%.[2] The investigator reported no change in cholesterol ester transfer protein (CETP) mass, but a significant increase in CETP activity was observed, suggesting an increased redistribution of TG and cholesterol esters between VLDL and HDL, respectively.[2] This leads to an increase in the cholesterol content of the VLDL and LDL particles and decrease in HDL-C levels. Interestingly, isotretinoin, a retinoic acid receptor agonist, which also induces hypertriglyceridemia and low HDL-C levels, has also been shown to increase CETP activity.[7] Therefore, increasing CETP activity might be the main mechanism for bexarotene-induced extreme lowering of HDL-C in our patient. However, other possibilities such as inactivation of ATP-binding cassette transporter A1 or lecithin-cholesterol acyltransferase, and reduced production and increased catabolism of apo A1, have not been studied yet.