

# Probable Bexarotene Hepatotoxicity Associated With Transient Serum Antimitochondrial Antibodies

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## Abstract

Bexarotene is a retinoid X receptor agonist approved for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma. In clinical trials, its use has been associated with elevations in serum aminotransferase activities. This report describes a case of probable bexarotene-induced hepatocellular injury in a woman, which was originally misdiagnosed as primary biliary cirrhosis because of the transient presence of serum antimitochondrial antibodies. Liver biopsy showed portal and periportal inflammation, ceroid-laden macrophages and normal bile ducts. Serum aminotransferase activities returned to normal approximately 8 weeks after discontinuing bexarotene and serum antimitochondrial antibodies were not detectable approximately one year after stopping the drug. This case reinforces the need to consider the possibility of drug-induced liver injury in patients taking bexarotene and that serum antimitochondrial antibodies may be transiently detectable in such individuals.

**Keywords:** Bexarotene; Hepatotoxicity; Antimitochondrial antibodies; Cutaneous T-cell lymphoma; Alzheimer disease

## Introduction

Bexarotene (Targretin<sup>®</sup>, Eisai Inc., Woodcliff Lake, NJ) is a retinoid X receptor-selective, antitumor retinoid approved by the U.S. Food and Drug Administration for the oral treatment

of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy [1]. In addition, bexarotene has received considerable recent attention because of a study claiming that it can clear beta-amyloid and reverse cognitive, social and olfactory deficits in a murine model of Alzheimer disease [2]. In clinical trials for cutaneous T-cell lymphoma, elevations in serum aminotransferase activities have been observed in up to 9% of subjects taking the drug with one possible case of liver failure [3-5]. Other than data from clinical trials and the manufacturer's package insert, there are no published cases on the presentation and features bexarotene-induced liver injury. This report describes a case of probable drug-induced liver injury in a woman with lymphomatoid papulosis who received bexarotene. Concurrent with acute drug-induced liver injury, the patient had transiently detectable serum antimitochondrial antibodies, leading to an initial misdiagnosis of primary biliary cirrhosis.

## Case Report

The patient was a physically fit 40 year-old woman with no family history of liver disease who drank only minimal quantities of alcohol. She was referred to Columbia University Medical Center for a second opinion regarding a possible diagnosis of primarily biliary cirrhosis. At approximately 8 years of age, she was diagnosed with lymphomatoid papulosis and received various forms of treatment intermittently, including psoralen-ultraviolet A phototherapy. About 12 years prior to presentation, she underwent radioiodine thyroid ablation for hyperthyroidism and has taken l-thyroxine since. At approximately age 40 she started treatment with bexarotene (225 mg/day). Approximately one month after starting bexarotene, her serum alkaline phosphatase and aminotransferase activities were normal. Approximately 5 months after starting treatment, her serum alkaline phosphatase was normal but alanine aminotransferase (ALT) was elevated at 259 IU/L and aspartate aminotransferase (AST) elevated at 187 IU/L; the serum bilirubin concentration was normal. At that time, her serum cholesterol was 262 mg/dl and serum triglycerides 395 mg/dl and she was started on fenofibrate. Approximately 8 months after starting bexaro-

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**Table 1.** CIOMS/RUCAM Scoring for Hepatotoxicity

| Type of liver injury                       | Hepatocellular (first exposure)               | Points |
|--|---|--------|
| Time of onset of the event                 | First exposure                                | -      |
| Time from drug intake until reaction onset | < 5 or > 90 days                              | + 1    |
| Course of the reaction                     | > 50% improvement 30 days                     | + 2    |
| Risk factors                               |   |        |
| Alcohol                                    | No  | + 0    |
| Age ≥ 55 years                             | No  | + 0    |
| Concomitant therapy                        | Time to onset incompatible                    | + 0    |
| Exclusion of nondrug-related causes        | Ruled out                                     | + 2    |
| Previous information on hepatotoxicity     | Reaction labeled in product's characteristics | + 2    |
| Response to re-administration              | Not available                                 | + 0    |
| Total score                                | Probable                                      | + 7    |

tene, alkaline phosphatase was normal but her serum ALT activity was elevated at 231 IU/L and AST activity elevated at 260 IU/L. Bexarotene and fenofibrate were discontinued and tests for hepatitis B surface antigen and antibodies against hepatitis C virus were negative. About two weeks after discontinuing bexarotene, the patient's serum alkaline phosphatase activity remained normal and her AST activity was 61 IU/L, ALT activity 88 IU/L and an ELISA for antimitochondrial M2 antibodies (performed at LabCorp) was positive (64.5 units). Approximately, six weeks after discontinuing bexarotene, her serum alkaline phosphatase, AST and ALT activities were normal and a repeat test for antimitochondrial M2 antibodies (performed at LabCorp) was again positive (49.2 units); a test for antinuclear antibodies was negative. A liver biopsy at that time showed portal and periportal inflammation and ceroid-laden macrophages primarily in centrilobular regions but the bile ducts were completely normal. The histological findings were most consistent with a resolving acute injury, such as a drug-induced injury. Two months after her liver biopsy, the patient's serum alkaline phosphatase activity was again normal and her serum immunoglobulin M concentration was normal. Approximately one year and again approximately 14 months after discontinuing bexarotene, tests for antimitochondrial antibodies (performed at Warde Medical Laboratory) were negative. Use of the CIOMS/RUCAM scale [6] predicted it was probable that the patient's liver damage was attributed to bexarotene (Table 1).

## Discussion

This case report emphasizes the possibility of an acute hepatocellular injury induced by bexarotene. Elevations in serum aminotransferase activities have been reported in clinical trials and are noted in the package insert for this drug. One case of liver failure was reported in a clinical trial of bexarotene; however, the patient had multiple possible etiologies for liver failure and the clinical picture was cholestatic without evidence of hepatocellular injury [3]. Otherwise, there have been no case reports in the medical literature describing the clinical presentation and features of a patient with bexarotene-induced hepatocellular toxicity.

The patient described in this case report was referred for a second opinion regarding a possible diagnosis of primary biliary cirrhosis, which was prompted by the detection of serum antimitochondrial antibodies soon after she discontinued bexarotene. A diagnosis of primary biliary cirrhosis was essentially eliminated because she never had an abnormally elevated serum alkaline phosphatase activity, did not have an elevated serum immunoglobulin M concentration and did not have any consistent histological features on liver biopsy. Approximately one year after discontinuing bexarotene, serum antimitochondrial antibodies were no longer detectable. Serum antimitochondrial antibodies are detected in approximately 40% of subjects with acute liver failure from a variety of causes, with disappearance in most subjects within one year after resolution [7]. Transiently detectable serum

antimitochondrial antibodies have also been reported in subjects with liver damage presumably induced by *Teucrium chamaedrys* (germander) [8] and an anticonvulsant [9]. In addition, antibodies against various cytosolic organelles, including mitochondria, have been reported in hepatitis induced by a variety of other drugs [10].

No single case report can prove cause and effect. Another limitation of this report is that antimitochondrial antibodies were measured in clinical reference laboratories and not in a research laboratory where reactivity to specific protein epitopes can be determined. Nonetheless, this case provides further evidence that bexarotene can induce liver injury in susceptible individuals. It also suggests that various types of liver damage could potentially lead to the generation of antimitochondrial antibodies but, as hypothesized by Leung et al [7], the pathogenesis of primary biliary cirrhosis requires additional factors.

### Conflict of Interest

None.

### Declaration of Funding

None.

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