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# Isotretinoin

Updated: May 1, 2018.

# OVERVIEW

## Introduction

Isotretinoin is a vitamin A derivative used in the treatment of severe acne and some forms of skin, head and neck cancer. Isotretinoin, like many retinoids, can lead to increase in serum aminotransferase levels, but, unlike acitretin and etretinate, isotretinoin has not been clearly implicated in cases of clinically apparent acute liver injury with jaundice.

## Background

Isotretinoin (eye" soe tret' i noyn), also known as 13-cis-retinoic acid, is an aromatic retinoid similar to vitamin A which is effective in treating refractory nodular acne and other disorders of keratinization. Unlike vitamin A, isotretinoin is not stored in the liver and is not associated with many of the toxic effects of high dose vitamin A therapy. Its mechanism of action in acne is believed to be mediated by activation of retinoic acid and retinoid X receptors, which regulate gene expression important in normalizing cell growth and differentiation. Isotretinoin is considered a second generation retinoid and its relative lack of receptor specificity accounts for its adverse side effects. All oral retinoids are potent teratogens and must be avoided or used with extreme caution in women of childbearing potential. Isotretinoin was approved for use in acne in the United States in 1982 and it is currently used, but only under strict requirements for monitoring and birth control. Indications are limited to severe nodular acne in a patient who has failed to respond to conventional therapy including systemic antibiotics. Isotretinoin is available in generic forms and under several brand names (Absorica, Amnesteem, Claravis, Myorisan, Sotret, Zenatane and previously Accutane) in capsules of 10, 20, 30 and 40 mg, the usual dose in adults being 0.5 to 2.0 mg/kg per day given in two divided doses for 15 to 20 weeks. Higher doses have been used in treatment of head and neck cancers. Side effects are common and include dry skin, nose bleeds, conjunctivitis and hair loss. Use of isotretinoin has also been linked to worsening of hyperlipidemia, hyperostosis, vision and hearing loss, pancreatitis, pseudotumor cerebri, birth defects, depression and suicide.

## Hepatotoxicity

Liver test abnormalities occur in up to 15% of patients on isotretinoin, although marked elevations above three times the upper limit of normal or requiring drug discontinuation are rare (<1%). The liver test abnormalities are typically asymptomatic and transient and can resolve even with continuing therapy. Clinically apparent liver injury due to isotretinoin is exceedingly rare, if it occurs at all. The acute liver injury with signs of hypersensitivity that occurs with etretinate and acitretin has not been described with isotretinoin therapy. Vitamin A-like effects on the liver with accumulation of lipids in nonparenchymal stellate cells has been described in rare patients on isotretinoin therapy, but the role of supplementary use of vitamin A in these cases

was not ruled out. Thus, the majority of reported cases of liver injury attibuted to isotretinoin have been anicteric and minimally symptomatic, but the lack of more severe hepatitis with jaundice may be due to the close monitoring and early discontinuation of isotretinoin which is required in the use of this agent for acne.

Likelihood score: C (probable cause of clinically apparent liver injury).

## Mechanism of Injury

The mechanism by which isotretinoin causes serum aminotransferase elevations is not known, but it may represent a direct toxic effect, in that it appears to be more frequent with higher dose therapy.

## Outcome and Management

Monitoring of liver tests is recommended for patients receiving isotretinoin at weekly or biweekly intervals. The serum aminotransferase elevations that occur during treatment are usually self-limited and do not always require dose modification or discontinuation of therapy. However, de novo elevations in serum aminotransferase levels of more than 5 times the upper limit of normal should prompt at least temporary discontinuation particularly if confirmed on a second sample or if accompanied by symptoms or jaundice. Patients with acitretin or etretinate associated acute liver injury have been found to tolerate isotretinoin without recurrence of liver injury, although isotretinoin is not approved and may not be as effective as acitretin in treating psoriasis.

References to isotretinoin hepatotoxicity are given in the Overview section on Retinoids (last updated May 2018).

Drug Class: Dermatologic Agents; Vitamins

Other Drugs in the Subclass:

- Vitamin A
- Retinoids
  - Acitretin
  - Etretinate
  - Isotretinoin

# CASE REPORT

## Case 1. Acute anicteric hepatitis with autoimmune features due to isotretinoin.

[Modified from: Guzman Rojas P, Gallegos Lopez R, Ciliotta Chehade A, Scavino Y, Morales A, Tagle M. [Autoimmune hepatitis induced by isotretionine]. Rev Gastroenterol Peru. 2016; 36: 86-9. Spanish. PubMed Citation]

A 16 year old adolescent female was found to have serum aminotransferase elevations 11 weeks after starting isotretinoin for severe acne. She had no history of liver disease, drug allergies, risk factors for viral hepatitis or alcohol use. Her past medical history included Hashimoto thyroiditis and hypothyroidism for which she took levothyroxine (50 mg daily). She was taking no other medications including over-the-counter products and herbal supplements. She had no symptoms of liver disease and the elevations were identified during routine monitoring of the isotretinoin therapy. Physical examination showed no evidence of hepatomegaly, abdominal tenderness or jaundice. Laboratory tests showed a serum ALT of 853 [22.4 times ULN], AST 501 U/L [12.5 times ULN], alkaline phosphatase 48 U/L [normal <340], and bilirubin 0.3 mg/dL [direct 0.10]. The R ratio was 22. The following week the ALT had risen to 1199 U/L and AST to 756 U/L, and isotretinoin was stopped (Table). Serum bilirubin remained normal, albumin was 4.3 g/dL, globulins 2.9 g/dL and INR 1.1. Tests for hepatitis A, B,

C and E were negative. While serum SMA was negative, ANA was positive in a titer of 1:160 and IgG was mildly elevated [1659 mg/dL, normal 700-1550 mg/dL]. Abdominal ultrasonography showed no evidence of biliary obstruction and no organomegaly or hepatic masses. A liver biopsy showed focal hepatocyte degeneration and parenchymal lymphocytic infiltration as well as mild portal inflammation and mild interface hepatitis. Because of the possibility of autoimmune hepatitis, she was started on prednisone (40 mg daily) to which azathioprine was added 2 weeks later. The serum aminotransferase levels rapidly improved and were normal 6 weeks after starting therapy. The prednisone was gradually reduced in dosage and eventually discontinued. The liver tests remained normal thereafter; isotretinoin was not restarted.

## Key Points

| | |
|---|---|
| Medication: | Isotretinoin (20 mg twice daily) |
| Pattern: | Hepatocellular (peak R=32) |
| Severity: | 1+ (anicteric) |
| Latency: | 11 weeks |
| Recovery: | 8 weeks |
| Other medications: | Levothyroxine |

## Laboratory Values

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Comments |
|---|---|---|---|---|---|
| Pre | 0 | 26 | 43 | 0.4 | Isotretinoin started |
| 11 weeks | 0 | 853 | 48 | 0.3 | Asymptomatic |
| 12 weeks | 0 | 1199 | 114 | 0.4 | Isotretinoin stopped |
| 14 weeks | 2 weeks | 327 | 105 | 0.3 | Pred 40 mg/d |
| 15 weeks | 3 weeks | 123 | 78 | 0.3 | Azathioprine added |
| 17 weeks | 5 weeks | 68 | 52 | 0.3 | Pred dose reduced |
| 19 weeks | 7 weeks | 41 | 29 | 0.3 | |
| 5 months | 2 months | 40 | 23 | 0.4 | Pred 5 mg/d |
| 6 months | 3 months | 24 | 19 | 0.3 | |
| 1.5 years | 1 year | 23 | 41 | 0.7 | No Pred or Azathioprine |
| 2 years | 2 years | 16 | 40 | 0.4 | |
| 3 years | 3 years | 25 | 31 | 0.4 | |
| **Normal Values** | | **<38** | **<340** | **<1.2** | |

## Comment

An acute anicteric hepatitis arose during isoretretinoin therapy in an adolescent girl with acne and a history of autoimmune thyroid disease. The hepatitis was asymptomatic, but ALT levels rose to 32 times ULN and the drug was stopped. Testing revealed a high titer of ANA and mild immunoglobulin elevations prompting a liver biopsy that was read as compatible with autoimmune hepatitis. She was treated with prednisone and azathioprine and liver tests fell to normal within 6 to 8 weeks. The dose of prednisone was gradually decreased and both prednisone and azathoprine were subsequently discontinued. She was followed carefully thereafter, and liver tests remained normal. This case nicely demonstrates the marked serum aminotransferase elevations that can occur during isotretinoin therapy. Unique in this case was the accompanying autoimmune features which led to use of immunosuppression. Importantly, prednisone and azathioprine were subsequently reduced in dose and

then discontinued. Liver tests remained normal indicating that the injury was probably drug induced liver injury with autoimmune features rather than spontaneous autoimmune hepatitis. [Addition details and test results kindly provided by Dr. Patricia Guzman.]

## PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Isotretinoin – Generic, Accutane®

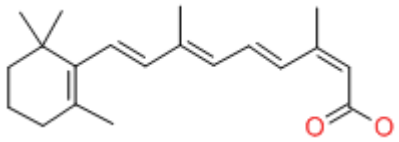
**DRUG CLASS**

Dermatologic Agents (Isotretinoin)

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Isotretinoin | 4759-48-2 | C20-H28-O2 |  |