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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Acitretin. [Updated 2015 Sep 1].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Acitretin

Updated: September 1, 2015.

OVERVIEW

Introduction

Acitretin is a vitamin A derivative currently used in the treatment of psoriasis. Acitretin, like many retinoids, can lead to increase in serum aminotransferase levels and has been implicated in cases of acute liver injury which can be severe and even fatal.

Background

Acitretin (a" si tre' tin) is an aromatic retinoid and the major metabolite of etretinate (e tret' i nate). Acitretin has replaced etretinate in clinical practice in the therapy of psoriasis because of its more favorable pharmacokinetics and half-life. Its mechanism of action in psoriasis is believed to be mediated by activation of retinoic acid and retinoid X receptors, which regulate gene expression important in growth and differentiation. Acitretin is considered a second generation retinoid and its relative lack of receptor specificity accounts for its many adverse side effects. All oral retinoids are potent teratogens and must be avoided or used with extreme caution in women of childbearing potential. Acitretin was approved for use in psoriasis and acne in the United States in 1996, but is currently used only in therapy of severe psoriasis unresponsive to conventional therapies and under strict regulations regarding monitoring and birth control. Acitretin is available generically and under the brand name of Soriatane in capsules of 10, 17.5, 22.5 and 25 mg, the usual dose in adults being 25 to 50 mg per day. Common side effects include dry skin, nose bleeds, conjunctivitis and hair loss. Acitretin is a known teratogen and embryotoxin.

Hepatotoxicity

Liver test abnormalities occur in up to one third of patients on acitretin, although marked elevations above three times the upper limit of normal occur in only 1% to 5%. These abnormalities are typically transient, not accompanied by symptoms and can resolve even with continuation of acitretin, but they may be associated with mild symptoms and require drug discontinuation in up to 4% of patients.

Acitretin can also cause clinically apparent liver injury with symptoms and jaundice. Although uncommon, acute liver injury from acitretin is well described and is estimated to occur in 0.1% to 0.5% of treated patients. The onset of injury can be as soon as one week or up to 9 months after starting therapy. The pattern of liver enzyme elevations is typically hepatocellular (Case 1), but cholestatic hepatitis due to acitretin has been reported (Case 2). Most cases resolve rapidly with stopping acitretin. Rash, fever, eosinophilia and other signs of hypersensitivity occur in many but not all cases; autoantibodies are rare. The injury is not at all like that of vitamin A and is not associated with fat accumulation in stellate cells. Because its potential for causing hepatotoxicity, routine monitoring of serum aminotransferase levels during acitretin therapy is recommended.

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

A similar pattern of acute liver injury was reported with etretinate, a related retinoid that was previously used for psoriasis and acne, but was withdrawn from use in the United States in 1998.

Likelihood score, etretinate: B (highly likely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which acitretin causes serum aminotransferase elevation is not known. The injury does not resemble that of hypervitaminosis A and excess acitretin is not stored in the liver or in stellate cells as is vitamin A. The rare clinically apparent cases of hepatotoxicity are likely due to hypersensitivity.

Outcome and Management

The serum aminotransferase elevations that occur on acitretin therapy are usually self-limited and may not require dose modification or discontinuation of therapy. However, persistent ALT or AST elevations above 3 times the upper limit of the normal range (ULN) should lead to dose adjustment or discontinuation. Any ALT elevation above 10 times the ULN or ALT elevations with symptoms or jaundice should lead to immediate discontinuation (Case 1). The acute clinically apparent liver injury caused by acitretin is typically self-limited and benign but fatal instances (particularly with overdose or use of high doses of acitretin) have been reported. Concurrent therapy with methotrexate may increase the risk of hepatotoxicity from acitretin. No instances of chronic hepatitis or vanishing bile duct syndrome due to acitretin have been reported. Restarting acitretin after clinically apparent liver injury is usually followed by recurrence and should be avoided.

References to the safety and potental hepatotoxicity of acitretin and etretinate are given in the Overview section on Retinoids (Last updated: September 2015).

Drug Class: Dermatologic Agents; Vitamins

Other Drugs in the Subclass, Vitamin A & Retinoids:

- Vitamin A
- Retinoids
  - Acitretin
  - Etretinate
  - Isotretinoin

CASE REPORTS

Case 1. Mild acute hepatitis due to acitretin.

[Modified from a case in the database of the Drug-Induced Liver Injury Network.]

A 66 year old man was found to have elevations in serum aminotransferase levels during routine monitoring 9 months after starting acitretin (50 mg daily) for pityriasis rubra psoriaform. He had no symptoms of liver disease and felt well. Past medical history included rheumatoid arthritis for which he took acetaminophen intermittently and occasional courses of prednisone, the most recent course being a few weeks before recognition of the liver injury. He used hydroxyzine regularly for itching due to his skin disease. He did not drink alcohol and had no history of liver disease, exposures to jaundiced individuals or risk factors for viral hepatitis. Physical examination was unrevealing and he had no apparent jaundice, rash, fever or signs of chronic liver disease. Laboratory testing showed marked elevations in serum ALT (1015 U/L) and AST (893 U/L), with minimal increase in alkaline phosphatase (Alk P: 212 U/L) and mild hyperbilirubinemia (2.9 mg/dL). The serum albumin

(3.9 g/dL) and prothrombin time (11.2 seconds) were normal. Serum creatinine was normal, and there was no eosinophilia. Tests for hepatitis A, B and C were negative. Serum ANA and AMA were strongly positive, but he was known to have serum autoantibodies previously. Hepatic imaging was not done. Acitretin was discontinued and laboratory results improved rapidly and were normal when he was seen 8 months later (Table).

Key Points

Medication:	Acitretin (50 mg daily)
Pattern:	Hepatocellular (R=13.2)
Severity:	2+ (jaundice not requiring hospitalization)
Latency:	9 months
Recovery:	4 weeks
Other medications:	Hydroxyzine, acetaminophen

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Comments
1 month	0	37	54	0.7	Routine monitoring
5 months	0	44	68	0.6	
6 months	0	20	68	0.5	
7 months	0	28	68	0.6	
8 months	0	56	82	0.6	
9 months	0	1015	212	2.9	No symptoms
Acitretin discontinued because of abnormal liver tests					
9.5 months	2 weeks	500	183	1.9	
10 months	4 weeks	41	99	0.6	
1.5 years	9 months	12	82	0.6	
Normal Values		**<45**	**<125**	**<1.2**	

Comment

The laboratory abnormalities (hepatocellular pattern of serum enzyme elevations) and clinical course (prompt resolution with stopping therapy) were compatible with acitretin induced liver disease. These abnormalities were detected during routine screening for possible liver injury in an asymptomatic patient on acitretin. The height of the elevations (>10 times ULN) and the presence of hyperbilirubinemia called for immediate discontinuation of acitretin.

Case 2. Severe acute hepatitis due to acitretin.

[Modified from a case in the database of the Drug-Induced Liver Injury Network.]

A 58 year old man developed fatigue, anorexia, nausea and dark urine followed pruritus and jaundice 4 months after starting acitretin (50 mg daily) for psoriasis. Past medical history was otherwise unremarkable. He did not drink alcohol and had no history of liver disease or risk factors for viral hepatitis. He was also taking omeprazole which he had been taking for several years for gastroesophageal reflux. He had taken minocycline for several months but had discontinued it several weeks before becoming ill. Laboratory testing showed mild jaundice (bilirubin 4.4 mg/dL) and elevations in serum aminotransferase levels (ALT 600 U/L, AST 252 U/L) and alkaline

phosphatase (Alk P: 256 U/L). The serum albumin (4.0 g/dL) and prothrombin time (INR 0.9) were normal. Acetretin was stopped promptly and he was admitted to the hospital for evaluation and monitoring (Table). Tests for hepatitis A, B, C and E were negative as were routine autoantibodies. Over the next 4 weeks his serum bilirubin continued to rise, peaking at 28.5 mg/dL. Itching was treated with cholestyramine and doxepin. Abdominal CT scans showed no evidence of biliary obstruction or hepatic masses. A liver biopsy showed severe cholestatic hepatitis suggestive of drug induced liver injury. Importantly, there was no bile duct injury or loss. He remained jaundiced for almost three months, but gradually improved and when seen in follow up 7 months after onset, he was asymptomatic and all liver tests were normal.

Key Points

Medication:	Acitretin (50 mg daily)
Pattern:	Hepatocellular (R=7.0) initially, cholestatic (R<1) later
Severity:	3+ (jaundice, hospitalization)
Latency:	5 months
Recovery:	4 months
Other medications:	Omeprazole

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Comments
5 months	0	600	256	4.4	R=7.0, acitretin stopped
	1 day	310	145	5.2	R=3.8, CT scan
	6 days	286	317	8.8	
	13 days	111	395	14.1	R=0.9
	19 days	62	425	20.2	
6 months	27 days	59	438	24.3	Severe pruritus
	33 days	62	488	27.3	INR 1.0
	35 days	76	462	28.5	Liver biopsy
	41 days	79	412	23.2	
7 months	62 days	86	156	6.8	
	76 days	75	138	3.6	
8 months	3 months	46	109	1.3	
1 year	7 months	42	85	1.2	
Normal Values		**<45**	**<125**	**<1.2**	

Comment

This patient suffered a somewhat severe and protracted cholestatic hepatitis which arose 5 months after starting acitretin. Despite stopping the medication, he continued to have worsening jaundice for several weeks. Laboratory, radiologic and histologic evaluations revealed no other cause of liver injury. He was treated symptomatically and did not receive corticosteroids, eventualy recovering completely. The pattern of liver injury was categorized as hepatocellular with a R ratio of 7.0 initally, but serum aminotransferase levels fell promptly and alkaline phosphatase values rose so that the pattern was distinctly cholestatic after the first week. The presence of pruritus and liver histology confirmed the cholestatic nature of the hepatitis.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Acitretin – Soriatane®

DRUG CLASS

Dermatologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Acitretin	55079-83-9	C21-H26-O3