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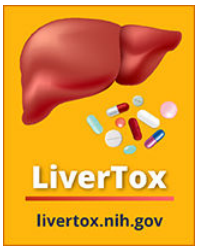

Retinoids

Updated: November 10, 2020.

OVERVIEW

Retinoids are both natural and synthetic derivatives of vitamin A, several of which have been developed for medical uses, largely to replace vitamin A which in high, therapeutic doses is associated with considerable toxicity. Retinoids have multiple actions and play important roles in regulation of cell proliferation and differentiation, vision, bone growth, tumor suppression and immunity. The effects of retinoids are thought to be mediated by their binding to and activation of the retinoic acid and retinoid X receptors which regulate gene expression, important in normal growth and differentiation. Vitamin A in doses that have medical effects was found to be toxic, particularly when given long term. Modification of the vitamin A structure led to retinoid molecules that had many of its beneficial, but fewer of its adverse effects.

Oral retinoids in use in the United States include acitretin for psoriasis and isotretinoin for severe nodular acne. Tretinoin is used topically and several other retinoids have been developed for therapy of uncommon forms of cancer (alitretinoin, bexarotene). The commonly used retinoids have many of the side effects of vitamin A including dry skin, cheilosis and nosebleeds and hair loss, but are not stored in the liver and do not cause the typical form of chronic liver disease associated with excessive vitamin A intake. Both acitretin and isotretinoin are teratogenic and embryotoxic and are contraindicated in women who are or intend to become pregnant. Retinoids have been implicated in causing mild-to-moderate elevations in routine liver tests, but these elevations are usually asymptomatic and transient, resolving spontaneously even with continued therapy. Marked elevations in serum aminotransferase levels during retinoid therapy are uncommon, and dose adjustment or drug discontinuation are rarely required for liver test abnormalities. Nevertheless, laboratory monitoring is recommended with routine liver tests at baseline and one month later, and testing thereafter only if abnormalities were found or symptoms arise. Several retinoids (acitretin, etretinate, retinal acetate) have been associated with a clinically apparent acute liver injury which typically arises during the first 3 months of therapy, has many features of hypersensitivity and can be severe and even fatal. Interestingly, isotretinoin often causes mild serum aminotransferase elevations and is commonly listed as having frequent adverse effects on the liver, but it has not been convincingly linked to instances of severe clinically apparent, acute liver injury with jaundice.

Two retinoids used in dermatology, acitretin and isotretinoin, are discussed in separate chapters; etretinate is discussed with acitretin which has replaced it in clinical practice. General references are provided below. References to the discussed retinoids are given in the annotate bibliographies of the individual chapters

Drug Class: Dermatologic Agents; Vitamins

Other Drugs in the Subclass:

- Vitamin A
- Retinoids

- Acitretin, Etretinate
- Isotretinoin
- Bexarotene

ANNOTATED BIBLIOGRAPHY

References updated: 10 November 2020

Zimmerman HJ. Vitamin A (retinol). Drugs used in dermatotherapy. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 727-9.

(Expert review of hepatotoxicity of vitamin A and the retinoids published in 1999; mentions two published reports of acute necrosis due to acitretin).

Liu LU, Schiano TD. Vitamin A (retinol). Hepatotoxicity of herbal medications, vitamins and natural hepatotoxins. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 744-6.

(Review of vitamin A and retinoid hepatotoxicity published in 2007).

Sewell MJ, Burkhart C, Morrell D. Dermatological pharmacology. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1271-96.

(Textbook of pharmacology and therapeutics).

Peck GL, Olsen TG, Yoder FW, Strauss JS, Downing DT, Pandya M, Butkus D, et al. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med. 1979;300:329–33. PubMed PMID: 153472.

(Initial report on use of isotretinoin for severe acne mentions that mild and transient ALT elevations occurred in one of the 14 patients treated for 4 months).

Thune P, Mork NJ. A case of centrolobular toxic necrosis of the liver due to aromatic retinoid--Tigason (Ro-10-9359). Dermatologica. 1980;160:405–8. PubMed PMID: 7389973.

(54 year old woman with ichthyosis developed fatigue 2-3 months after starting etretinate [peak bilirubin 2.6 mg/dL, ALT 1260 U/L, Alk P 350 U/L], biopsy showing centrolobular necrosis, with slow resolution over the next 6 months).

Peck GL, Olsen TG, Butkus D, Pandya M, Arnaud-Battandier J, Gross EG, Windhorst DB, et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. J Am Acad Dermatol. 1982;6 Suppl:735–45. PubMed PMID: 6461677.

(Controlled trial of 4 months of isotretinoin in 33 patients with severe acne showed dramatic therapeutic effect; side effects were dry skin, eyes and nasal membranes and dermatitis; ALT elevations occurred in 3 patients [10%], but levels returned to normal despite continuing and no patient stopped therapy because of side effects).

Olson JA. Adverse effects of large doses of vitamin A and retinoids. Semin Oncol. 1983;10:290–3. PubMed PMID: 6364354.

(Review of retinoids and vitamin A which do not share same toxicity, but usually have a low therapeutic-toxic index).

Ward A, Brogden RN, Heel RC, Speight TM, Avery GS. Isotretinoin. A review of its pharmacological properties and therapeutic efficacy in acne and other skin disorders. Drugs. 1984;28:6–37. PubMed PMID: 6235105.

(Review of pharmacology, efficacy and safety of isotretinoin: elevations in liver tests occur in 10% of patients, "although these changes rarely reach statistical or clinical significant levels").

Strauss JS, Rapini RP, Shalita AR, Konecky E, Pochi PE, Comite H, Exner JH. Isotretinoin therapy for acne: results of a multicenter dose-response study. J Am Acad Dermatol. 1984;10:490–6. PubMed PMID: 6233335.

(150 patients with nodulocystic acne were treated with one of 3 doses of isotretinoin [0.1, 0.5 or 1.0 mg/kg/day] for 20 weeks; side effects were common [dry skin, nosebleeds, hair loss, headache], mean ALT and AST values increased slightly in the highest dose group, and AST increases occurred in 15-18% of patients, but did not lead to dose modification or clinical symptoms).

Heller EH, Shiffman NJ. Synthetic retinoids in dermatology. Can Med Assoc J. 1985;132:1129–36. PubMed PMID: 3158386.

(Discussion of two synthetic analogues of vitamin A introduced into dermatology: isotretinoin [used in acne] and etretinate [used in psoriasis]; these retinoids are less toxic than vitamin A and not stored in the liver, although they are metabolized there; minor liver test abnormalities may arise during therapy, but rarely required dose modification).

Vahlquist A. LöL, Nordlinder H, Rollman O, Vahlquist C. Differential hepatotoxicity of two oral retinoids (etretinate and isotretinoin) in a patient with palmoplantar psoriasis. Acta Derm Venereol. 1985;65:359–62. PubMed PMID: 2413699.

(64 year old woman was found to have abnormal liver tests 5 months after starting etretinate [bilirubin 0.7 mg/dL, ALT 950 U/L, Alk P 402 U/L], liver biopsy showing hepatitis without steatosis, resolving with stopping and prednisone therapy, recurring upon rechallenge, but not when isotretinoin was started which was less effective for the psoriasis).

Yob EH, Pochi PE. Side effects and long-term toxicity of synthetic retinoids. Arch Dermatol. 1987;123:1375–8. PubMed PMID: 3310911.

(Retinoids are modifications of vitamin A molecule and are not stored in the liver; hepatotoxicity of retinoids is different from that of vitamin A, usually arising within first 1-2 months and having features of hypersensitivity).

Larrey D, Fréaux E, Babany G, Berson A, Amée-Manesme O, Degott C, Bettan L, et al. Gastroenterol Clin Biol. 1988;12:240–4. [Hepatitis probably caused by Plethoryl. Apropos of 7 cases]. French. PubMed PMID: 3371597.

(Seven cases of liver injury in women taking Plethoryl [a retinoid containing combination used to treat obesity], arising after 3-16 weeks of therapy [bilirubin 3.3-26.3 mg/dL, ALT 21-61 times ULN, Alk P 0.9-1.8 times ULN], resolving within 2-3 months of stopping).

David M, Hodak E, Lowe NJ. Adverse effects of retinoids. Med Toxicol Adverse Drug Exp. 1988;3:273–88. PubMed PMID: 3054426.

(Review of pharmacology, clinical effectiveness and low dose, long term toxicities of the retinoids; states that therapy usually has little effect on ALT or bilirubin levels).

Roenigk HH Jr. Liver toxicity of retinoid therapy. J Am Acad Dermatol. 1988;19(1 Pt 2):199–208. PubMed PMID: 3045164.

(Review of hepatotoxicity of vitamin A and the retinoids).

Kragballe K, Jansen CT, Geiger JM, Bjerke JR, Falk ES, Gip L, Hjorth N, et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study. Acta Derm Venereol. 1989;69:35–40. PubMed PMID: 2563606.

(Controlled trial of acitretin [n=127] vs etretinate [n=41] in psoriasis found similar efficacy; AST elevations occurred in 12% vs 11% and one patient on acitretin for 12 weeks developed biopsy proven "toxic hepatitis" which resolved on stopping).

Fallon MB, Boyer JL. Hepatic toxicity of vitamin A and synthetic retinoids. J Gastroenterol Hepatol. 1990;5:334–42. PubMed PMID: 2103414.

(Review of liver injury due to hypervitaminosis A and retinoids identified 18 reports of vitamin A hepatotoxicity in the English literature, patient ages 6 to 63 years, presenting with rash, fatigue, hepatomegaly and hepatic synthetic dysfunction, biopsy showing fat in stellate cells and fibrosis; little evidence that isotretinoin causes liver injury other than mild rapidly reversible ALT elevations; etretinate causes ALT elevations in ~20% of patients and case reports of clinically apparent injury have been published, but vary in clinical patterns).

Vahlquist A. Long-term safety of retinoid therapy. J Am Acad Dermatol. 1992;27(6 Pt 2):S29–33. PubMed PMID: 1460122.

(Patients have been treated with retinoids for up to 15 years, generally without toxicity; retinoids do not accumulate in the liver and do not cause accumulation of fat droplets in stellate cells as occurs with hypervitaminosis A; two types of hepatotoxicity, one idiosyncratic acute hepatitis typically occurring with aromatic retinoids and one a long term low grade injury that can lead to cirrhosis, perhaps aggravated by alcohol that the author claims can occur with all retinoids).

Pilkington T, Brodgen RN. Acitretin: a review of its pharmacology and therapeutic use. Drugs. 1992;43:597–627.

(Extensive review of the pharmacology, clinical efficacy, and toxicity of acitretin; vitamin A like side effects are common such as dry skin, lips, eyes and nose, skin desquamation, alopecia, fatigue and pruritus; ALT elevations occur in 16%, but are usually asymptomatic, although cases requiring drug withdrawal have been reported).

Barth JH, Macdonald-Hull SP, Mark J, Jones RG, Cunliffe WJ. Isotretinoin therapy for acne vulgaris: a re-evaluation of the need for measurements of plasma lipids and liver function tests. Br J Dermatol. 1993;129:704–7. PubMed PMID: 8286255.

(Retrospective analysis of 209 patients treated with isotretinoin found "no significant change in any of the tests of liver function", which led the authors to argue against the recommendation for routine monitoring of liver tests during therapy).

Coschieri M, Philippon A, Quinsat D, Dor JF, Chichmanian RM. Acute hepatitis involvement during ingestion of acitretin. Gastroenterol Clin Biol. 1993;17:769–70. PubMed PMID: 8288093.

(80 year old man developed nausea and rash one week after starting acitretin [bilirubin normal, ALT 21 times ULN, Alk P normal], resolving within a month of stopping).

Shibata K, Shimamoto Y, Ishibashi S, Tominaga H, Suga K, Yamaguchi M. Life-threatening hepatic toxicity caused by all-trans-retinoic acid in a patient with acute promyelocytic leukaemia. Clin Lab Haematol. 1994;16:191–5. PubMed PMID: 7955929.

(39 year old man with acute promyelocytic leukemia developed jaundice one month after starting all-trans-retinoic acid with peak bilirubin ~10 mg/dL, resolving in 18 days after stopping and patient achieving remission despite early discontinuation).

Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. J Am Acad Dermatol. 1999;41(3 Pt 2):S7–S12. PubMed PMID: 10459140.

(Review of side effects of acitretin based upon data from 1877 patients reported "overt chemical hepatitis" in 0.26%; among 128 patients undergoing routine pre- and post-treatment liver biopsies, 83% were improved or unchanged; authors recommend routine monitoring of liver tests every 1-2 weeks "until stable, and thereafter at intervals as clinically indicated").

Perea G, Salar A, Alté A, Brunet S, Sierra J. Acute hepatomegaly with severe liver toxicity due to all-trans-retinoic acid. Haematologica. 2000;85:551–2. PubMed PMID: 10800178.

(40 year old man with promyelocytic leukemia developed jaundice 21 days after starting all-trans-retinoic acid and idarubicin [direct bilirubin 2.3 mg/dL, ALT normal, Alk P 370 U/L], biopsy showing intrahepatic cholestasis and resolving within 2 weeks of stopping).

Mawson AR, Steele TA. Possible role of retinoids in hepatitis B virus-associated liver damage. Exp Biol Med (Maywood). 2001;226:734–9. PubMed PMID: 11520938.

(Review and hypothesis regarding interactions of vitamin A, retinoids and hepatitis B virus infection).

Van Zander J, Orlow SJ. Efficacy and safety of oral retinoids in psoriasis. Expert Opin Drug Saf. 2005;4:129–38. PubMed PMID: 15709903.

(Review of acitretin and other retinoids as therapy of psoriasis; side effects include ALT elevations in one third of treated patients, but clinically apparent liver injury is rare).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, one was attributed to acitretin: Case 1 for acitretin).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70:721–8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, isotretinoin was the most frequently mentioned agent [420 cases: 6.4%], but no information on the characteristics of the cases is provided).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to vitamin A or a retinoid).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, two of which were attributed to retinoids).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and Outcomes of 899 Patients With Drug-Induced Liver Injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 3 cases were attributed to acitretin, but none to other retinoids or vitamin A).

DeKlotz CMC, Roby KD, Friedlander SF. Dietary supplements, isotretinoin, and liver toxicity in adolescents: a retrospective case series. Pediatrics. 2017;140:e20152940. pii. PubMed PMID: 28864554.

(Eight adolescents with acne in an isotretinoin monitoring program were found to have mild elevations in serum aminotransferase levels [ALT 34-59 U/L, AST 41-187 U/L, bilirubin normal and Alk P not provided], but all

were also taking herbal and dietary supplements, including green tea, energy shakes and amino acids and creatine, and the elevations appeared to be more related to these products than the isotretinoin therapy).

Drugs for psoriasis. Med Lett Drugs Ther. 2019;61(1574):89–96. PubMed PMID: 31381544.

(Concise review of the drugs approved for use in psoriasis including their mechanism of action, clinical efficacy, safety and costs, mentions that acitretin has significant mucocutaneous toxicity with cheilitis, hair loss, dry skin and desquamation and that about one third of patients have ALT elevations during therapy that are usually mild and transient but can evolve into clinically significant liver injury and can lead to cirrhosis).

Barbieri JS, Frieden IJ, Nagler AR. Isotretinoin, patient safety, and patient-centered care-time to reform iPLEDGE. JAMA Dermatol. 2020;156:21–2. PubMed PMID: 31664426.

(Viewpoint on the FDA program restricting use of isotretinoin and requiring rigorous monitoring for birth control, mentions that pregnancy prevention programs are often ineffective but can be financially burdensome and interfere with appropriate therapy of severe acne; no discussion of ALT elevations or hepatotoxicity).