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Retinoids

Updated: May 1, 2018.

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 this record and their combined references of retinoids are provided at the end of this introductory section. The hepatotoxicity of vitamin A is discussed separately in another record.

Drug Class: Vitamins

Other Drugs in the Subclass, Vitamin A & Retinoids:

- Vitamin A
- Retinoids

- Acitretin, Etretinate, Isotretinoin
- Bexarotene

ANNOTATED BIBLIOGRAPHY

References updated: 01 May 2018

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).

Burkhart C, Morrell D, Goldsmith L. Dermatological pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 805-32.

(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 (4 Pt 2 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).

Glazer SD, Roenigk HH Jr, Yokoo H, Sparberg M. A study of potential hepatotoxicity of etretinate used in the treatment of psoriasis. J Am Acad Dermatol 1982; 6(4 Pt 2 Suppl): 683-7. PubMed PMID: 7068976.

(20 patients with psoriasis underwent liver biopsy before and/or up to 6 months after starting etretinate, 20% had ALT elevations, but no worsening of fibrosis or consistent effect on histology).

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).

Beck HI, Foged EK. Toxic hepatitis due to combination therapy with methotrexate and etretinate in psoriasis. Dermatologica 1983; 167: 94-6. PubMed PMID: 6628806.

(47 year old woman with psoriasis who had been on oral weekly methotrexate for 10 years with normal liver tests, developed fever, jaundice and ascites 4 months after adding 25-75 mg/day etretinate [bilirubin 17 mg/dL, AST 460 U/L, Alk P 1.5 times ULN, prothrombin index 27%], with resolution 2 months after stopping both agents; liver biopsy later showed cirrhosis).

Hennes R, Mack A, Schell H, Vogt HJ. 13-cis-retinoic acid in conglobate acne. A follow-up study of 14 trial centers. Arch Dermatol Res 1984; 276: 209-15. PubMed PMID: 6236757.

(Among 87 patients treated with isotretinoin for severe acne monitored for 12 to 21 months, sustained remissions occurred in 81% and all side effects resolved within 3 months of stopping; no mention of hepatotoxicity).

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").

Marsden JR, Trinick TR, Laker MF, Shuster S. Effects of isotretinoin on serum lipids and lipoproteins, liver and thyroid function. Clin Chim Acta 1984; 143: 243-51. PubMed PMID: 6238729.

(7 patients with rosacea were treated with isotretinoin for 16 weeks; average serum AST levels increased from 17 to 24 U/L and Alk P from 69 to 81 U/L, while bilirubin levels fell and no patient developed clinically apparent liver injury).

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).

Van Voorst-Vader PC, Houthoff HJ, Eggink HF, Gips CH. Etretinate (Tigason) hepatitis in 2 patients. Dermatologica 1984; 168: 41-6. PubMed PMID: 6698264.

(2 women with etretinate hepatotoxicity; 70 and 61 year olds with onset of liver tests abnormalities 6 and 3 months after starting etretinate [bilirubin normal, ALT 31 and 476 U/L, Alk P 166 and 147 U/L], resolving within 2-3 months of stopping and recurring within a month of rechallenge or switching to a lower dose [while ALT remaining mildly abnormal]).

Danan G, Pessayre D, Rueff B, Benhamou JP. [Acute hepatitis probably due to Plethoryl]. Gastroenterol Clin Biol 1984; 8: 770-1. French. PubMed PMID: 6549301.

(3 women, ages 25 to 44 years, developed symptoms of hepatitis 2 to 10 weeks after starting Plethoryl, a mixture including 50,000 IU of a retinoid marketed in Eruope for treatment of obesity [bilirubin 2.6-3.8 mg/dL, ALT 490-576 U/L, Alk P normal], resolving within 4-8 weeks of stopping).

Foged E, Bjerring P, Kragballe K, Sød H, Zachariae H. Histologic changes in the liver during etretinate treatment. J Am Acad Dermatol 1984; 11 (4 Pt 1): 580-3. PubMed PMID: 6490982.

(Among 32 patients treated with etretinate for 6 to 60 months undergoing liver biopsy, changes included mild fatty change, nuclear variability and minimal fibrosis, but similar changes were found in controls).

Weiss VC, West DP, Ackerman R, Robinson LA. Hepatotoxic reactions in a patient treated with etretinate. Arch Dermatol 1984; 120: 104-6. PubMed PMID: 6691707.

(74 year old woman developed fatigue and fever 1 month after starting etretinate [bilirubin normal, ALT 545 U/L, Alk P 265 U/L, eosinophils 14-24%], rapidly improving upon stopping and recurring within one month of restarting).

Gavish D, Katz M, Gottehrer N, Israeli A, Lijovetzky G, Holubar K. Cholestatic jaundice, an unusual side effect of etretinate. J Am Acad Dermatol 1985; 13: 669-70. PubMed PMID: 4078057.

(58 year old man with psoriasis developed jaundice and pruritus 12 weeks after starting etretinate [bilirubin rising to 23.4 mg/dL, ALT 60 U/L, Alk P 420 U/L], resolving within 4 weeks of stopping; biopsy showed cholestatic hepatitis).

Grimaud JC, Langier R, Costa-Legre MC, Payan MJ. [Hepatitis due to etretinate]. Presse Med 1985; 14: 844-5. French. PubMed PMID: 3158914.

(62 year old man with psoriasis developed abnormal serum enzyme levels 10 days after restarting etretinate which had been given for 3 months in the past [ALT 420 U/L, Alk P 176 U/L, bilirubin not given] resolving within 2 months of stopping).

Weiss VC, Layden T, Spinowitz A, Buys CM, Nemchausky BA, West DP, Emmons KM. Chronic active hepatitis associated with etretinate therapy. Br J Dermatol 1985; 112: 591-7. PubMed PMID: 4005158.

(39 year old man with psoriasis developed nausea 6 months after starting etretinate [bilirubin normal, ALT 495 U/L, Alk P 141 U/L], with persistence of ALT elevations for 6 months after stopping and biopsy showing "chronic active hepatitis").

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).

Atttali P, Bernuau J, Fabre M, Degott C, Ink O. [Fatal fulminant hepatitis probably due to Plethoryl]. Gastroenterol Clin Biol 1986; 10: 92. French. PubMed PMID: 3754231.

(22 year old developed fatigue 2 weeks and jaundice 3 weeks after strating Plethoryl, a combination drug for obesity which includes a retinoid [bilirubin 12.3 mg/dL, ALT 5,500 U/L], progressing to hepatic failure and death one month later).

Jean-Pastor MJ, Jean P, Biour M, Castot A, Chichmanian F, Danan G, Levy VG, et al. [Hepatopathies from treatment with a specialty drug combination of tiratricol-cyclovalone-retinol]. J Toxicol Clin Exp 1986; 6: 115-21. French. PubMed PMID: 3783484.

(Summary of 9 cases of liver injury attributed to use of Plethyl, 6 of which were considered convincing; all in obese women, ages 24 to 50 years with latency to onset of 2 weeks to 2 years, 3 with jaundice, all resolving after stopping and 3 recurring upon re-exposure, injury attributed to a retinol [50,000 IU] in the commercial product).

Marti R, Voiment YM, André M. [Acute hepatitis caused by Plethoryl]. Gastroenterol Clin Biol 1986; 10: 853. French. PubMed PMID: 3803829.

(36 year old woman developed fever and arthralgias 3 months after starting Plethoryl, a drug combination for obesity which includes a retinoid [bilirubin 4.0 mg/dL, ALT 708 U/L, Alk P 137 U/L], resolving rapidly upon stopping and recurring within 5 days of restarting).

Camuto P, Shupack J, Orbuch P, Tobias H, Sidhu G, Feiner H. Long-term effects of etretinate on the liver in psoriasis. Am J Surg Pathol 1987; 11: 30-7. PubMed PMID: 3789256.

(18 patients treated with etretinate for psoriasis for at least 5 years underwent liver biopsy; 2 had persistent liver test elevations; one had Alk P >500 U/L with a "normal" liver biopsy; one had ALT of 125 U/L with chronic hepatitis and fibrosis on biopsy [no HCV testing available]; a third had normal tests, but had cirrhosis on biopsy; many biopsies showed fatty change and occasional stellate cell hypertrophy).

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).

Khouri MR, Saul SH, Dlugoz AA, Soloway RD. Hepatocanalicular injury associated with vitamin A derivative etretinate. Dig Dis Sci 1987; 32: 1207-11. PubMed PMID: 3652901.

(73 year old man with psoriasis developed fever 3-4 weeks after starting etretinate [bilirubin 0.8 mg/dL, ALT 126 U/L, Alk P 383 U/L, eosinophils 1368/μL], jaundice arising with continuation of drug for 5 days [peak bilirubin 2.5 mg/dL], resolving within 2 weeks of stopping).

Kingston TP, Matt LH, Lowe NJ. Etretin therapy for severe psoriasis. Arch Dermatol 1987; 123: 55-8. PubMed PMID: 2948451.

(Open label study of etretin [acitretin] in 21 patients with psoriasis, 3 required dose modification for liver test elevations, but few details given).

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

Prudent A, Marchetti B, Philibert P, Lacroix G, Legré. [Acute recurrent hepatitis caused by plethoryl]. Ann Gastroenterol Hepatol (Paris) 1988; 24: 27. French. PubMed PMID: 3355100.

(48 year old woman developed nausea, fatigue, and arthralgias 6 month after starting Plethoryl for weight loss [bilirubin 2.2 mg/dL, ALT 588 U/L, Alk P 448 U/L] which resolved on stopping and recurred within a week of restarting on two occasions).

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).

Thirumoorthy T, Shupack JL. Adverse hepatic reactions associated with etretinate in patients with psoriasis--analysis of 22 cases. Ann Acad Med Singapore 1988; 17: 477-81. PubMed PMID: 3066276.

(Among 533 patients with psoriasis treated with etretinate, there were 22 reports of hepatic adverse events [4%]; 6 were considered probably related, 7 possibly, 6 unlikely and 3 unclassifiable; 2 patients developed fever, malaise and rash 4-5 weeks after starting etretinate with rapid rise in ALT and rapid resolution on stopping; others had serum enzyme elevations without symptoms or jaundice).

Zachariae H. Dangers of methotrexate/etretinate combination therapy. Lancet 1988; 1 (8582): 422. PubMed PMID: 2893228.

(2 of 10 patients on the combination of etretinate and methotrexate developed severe liver injury, including a 47 year old man who developed jaundice 1 month after adding etretinate to chronic methotrexate therapy [bilirubin 17.1 mg/dL, AST 305 U/L, Alk P 742 U/L], which resolved within 2 months of stopping both).

Causse X, Paliard P. [Hepatitis with auto-immunization probably caused by Plethoryl]. Gastroenterol Clin Biol 1989; 13: 526-7. French. PubMed PMID: 2753297.

(32 year old woman developed jaundice 4-6 weeks after starting Plethoryl for obesity [bilirubin 12.2 mg/dL, ALT 1690 U/L], but continued drug for 2 months and developed ANA 1:1024, responding to course of corticosteroid therapy; ultimately liver tests were normal and ANA fell to 1:40; Plethoryl [a drug combination that included a synthetic retinoid] was withdrawn from market in France in 1988).

Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. J Am Acad Dermatol 1989; 20: 1088-93. PubMed PMID: 2526824.

(Controlled trial of 4 different doses of acitretin in 38 patients with psoriasis, followed by open label long term use, 15% had ALT or AST elevations during therapy, rising above 100 U/L in two patients, without jaundice, and resolving rapidly on stopping).

Maroy B, Moullot P, Constantin JM. [Probable side effects caused by plethoryl. Common acute hepatitis, anicteric hepatitis, cirrhosis due to hypervitaminosis A, inflammatory arthralgias]. Presse Med 1989; 18: 567-70. French. PubMed PMID: 2523055.

(4 cases of adverse events due to use of Plethoryl, including 2 instances of acute hepatocellular injury, 1 of cirrhosis and 1 of arthritis which improved on stopping Plethoryl).

Roenigk HH Jr. Liver toxicity of retinoid therapy. Pharmacol Ther 1989; 40: 145-55. PubMed PMID: 2645587.

(Review of toxicity of retinoids including description of liver biopsy results described by Glazer [1982]).

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 Dermatol 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).

Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. J Am Acad Dermatol 1989; 21: 681-6. PubMed PMID: 2530251.

(Controlled trial of acitretin in 15 patients with psoriasis, including a 28 year old man who developed fatigue and elevated liver tests [bilirubin 0.5 mg/dL, ALT 396 U/L, Alk P 140 U/L], which resolved within 2 months of stopping).

van Ditzhuijsen TJ, van Haelst UJ, van Dooren-Greebe RJ, van de Kerkhof PC, Yap SH. Severe hepatotoxic reaction with progression to cirrhosis after use of a novel retinoid (acitretin). J Hepatol 1990; 11: 185-8. PubMed PMID: 2147707.

(50 year old woman with psoriasis developed elevated liver tests 4-5 months after starting acitretin [bilirubin normal, ALT 790 U/L, Alk P 166 U/L] and worsened for 2 months after stopping [bilirubin rising to 3.8 mg/dL]; liver biopsy showed severe hepatitis with bridging necrosis and, on follow up, an inactive cirrhosis despite all liver tests returning to normal).

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 6-63 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).

Marhold I, Duschet P, Schwarz T, Gschnait F. [Successful use of isotretinoin in type Zumbusch generalized pustular psoriasis following recovered etretinate-induced hepatitis]. Hautarzt 1991; 42: 580-3. German. PubMed PMID: 1938411.

(29 year old woman with psoriasis responded to etretinate but developed rising Alk P levels [172 to 1736 U/L] without jaundice and only mild ALT increases [38 to 178 U/L] 24 days after starting therapy, which improved on stopping and she later tolerated isotretinoin without recurrence [Alk P 118 U/L, ALT 14 U/L]).

Dubois A, Balducchi JP, Barbuat C, Fabre J, Flaisler F, Joujoux JM, Pignodel C, et al. [Portal hypertension and hypervitaminosis A. Apropos of 2 cases and review of the literature]. Rev Med Interne 1991; 12: 295-8. French. PubMed PMID: 1759070.

(Two patients presented with ascites and biopsy showing stellate cell hypertrophy one having taken methoxypsoralen [for tanning] and one Plethoryl [for weight loss] for several years, improving on stopping).

Navascués CA, Suáz A, Riestra S, Rodrigo L. [Hepatitis due to etretinate: a case report]. Med Clin (Barc) 1991; 96: 679. Spanish. PubMed PMID: 2056805.

(81 year old man treated with etretinate for psoriasis for 7 months developed jaundice [bilirubin 2.4 mg/dL, ALT 804 U/L, Alk P 3 times ULN, protime 17 seconds]).

Taylor AE, Mitchison H. Fatty liver following isotretinoin therapy. Br J Dermatol 1991; 124: 505-6. PubMed PMID: 2039732.

(18 year old male body builder developed elevated ALT levels [134 U/L] without jaundice during 6 month course of isotretinoin for acne; liver biopsy showed marked steatosis, but ALT levels remained high 20 months after stopping drug).

McElwee NE, Schumacher MC, Johnson SC, Weir TW, Greene SL, Scotvold MJ, Hunter JR, et al. An observational study of isotretinoin recipients treated for acne in a health maintenance organization. Arch Dermatol 1991; 127: 341-6. PubMed PMID: 1825596.

(Retrospective analysis of 466 patients treated with isotretinoin in a health care maintenance organization found 6 [1.8%] with moderate AST elevations [90-350 U/L], but levels often normalized despite drug continuation; isotretinoin stopped in 3 patients for liver tests abnormalities).

Green C, Lakshmipathi T. A case of hepatitis related to etretinate therapy and hepatitis B vaccine. Dermatologica 1991; 182; 119-20. PubMed PMID: 1828773.

(41 year old man with psoriasis had mild fluctuations in serum AST during etretinate therapy ultimately [at 9 months] rising to 361 U/L, without jaundice or symptoms and resolving rapidly with discontinuation).

Murray HE, Anhalt AW, Lessard R, Schacter RK, Ross JB, Stewart WD, Geiger JM. A 12-month treatment of severe psoriasis with acitretin: results of a Canadian open multicenter study. J Am Acad Dermatol 1991; 24: 598-602. PubMed PMID: 1827800.

(Open label study of 12 month course of acitretin in 63 patients with psoriasis, ALT elevations occurred in ~10% of patients, one requiring discontinuation [ALT 3 times ULN at 5 months, resolving within two months of stopping]).

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).

Mork NJ, Kolbenstvedt, Austad J. Efficacy and skeletal side effects of two year' acitretin treatment. Acta Dermatol Venereol 1992; 72: 445-8. PubMed PMID: 1362840.

(One of 51 patients with psoriasis treated with acitretin for up to 2 years developed "toxic hepatitis" which arose after 5 months of treatment and resolved 20 weeks after stopping; few details given).

Pilkington T, Brodgen RN. Acitretin: a review of its pharmacology and therapeutic use. Drugs 1992; 43: 597-627. PubMed PMID: 1377120.

(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).

Sanchez MR, Ross B, Rotterdam H, Salik J, Brodie R, Freedberg IM. Retinoid hepatitis. J Am Acad Dermatol 1993; 28 (5 Pt 2): 853-8. PubMed PMID: 8491880.

(65 year old woman developed elevated ALT levels 2 months after starting etretinate [bilirubin 2.9 rising to 6.7 mg/dL, ALT 820 U/L, Alk P 250 U/L], worsening for 2 months after stopping and then resolving).

Kano Y, Fukuda M, Shiohara T, Nagashima M. Cholestatic hepatitis occurring shortly after etretinate therapy. J Am Acad Dermatol 1994; 31: 133-4. PubMed PMID: 8021361.

(65 year old man with psoriasis developed fever and jaundice within 7 days of starting etretinate, resolving within 2 weeks of stopping; few details given).

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).

Krürasagakes S, Grabbe J, Czarnetzki BM. Possible aggravation of hepatitis A by acitretin. Acta Derm Venereol 1995; 75: 82-3. PubMed PMID: 7747547.

(49 year old man developed fatigue 1 month and fever and jaundice 2 months after starting acitretin [bilirubin ~12 mg/dL, ALT ~2500 U/L, Alk P normal, protime 50%], but was also IgM anti-HAV positive; authors hypothesize that acitretin like vitamin A may worsen the course of acute viral hepatitis).

Stern RS, Fitzgerald E, Ellis CN, Lowe N, Goldfarb MT, Baughman RD. The safety of etretinate as long-term therapy for psoriasis: results of the etretinate follow-up study. J Am Acad Dermatol 1995; 33: 44-52. PubMed PMID: 7601945.

(Analysis of prospective survey of 956 patients with psoriasis treated with etretinate for up to 5 years; 66 patients reported hepatic problems during study including 13 with hepatitis and 13 with cirrhosis [5 with both], but relationship to therapy could not be assessed).

Gunston G, Mehta U, van de Wal B. New warnings on the use of isotretinoin (Roaccutane). S Afr Med J 1998; 88: 1394. PubMed PMID: 9861942.

(Summary of warnings placed on isotretinoin regarding suicide and potential of liver test abnormalities; 15% of patients on therapy had some degree of liver test abnormality arising on therapy, mostly asymptomatic and resolving without altering dose).

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").

Roenigk HH Jr, Callen JP, Guzzo CA, Katz HI, Lowe N, Madison K, Nigra T, et al. Effects of acitretin on the liver. J Am Acad Dermatol 1999; 41: 584-8. PubMed PMID: 10495381.

(Among 128 patients treated with acitretin, 83 underwent liver biopsy before and 2 years after starting therapy; 30% had ALT elevations, liver histology did not change on average; one patient developed fibrosis, but had no serum enzyme worsening).

Perea G, Salar A, AltéA, 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 promyleocytic 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).

McLane J. Analysis of common side effects of isotretinoin. J Am Acad Dermatol 2001; 45: S188-94. PubMed PMID: 11606952.

(Prospective analysis of safety in two trials of isotretinoin in 369 patients with acne found no overall change in mean ALT levels "to a significant extent" and no episodes of hepatitis and jaundice; no mention of drug discontinuation for ALT elevations).

Alcalay J, Landau M, Zucker A. Analysis of laboratory data in acne patients treated with isotretinoin: is there really a need to perform routine laboratory tests? J Dermatolog Treat 2001; 12: 9-12. PubMed PMID: 12171680.

(Retrospective analysis of computerized medical files from 1292 patients treated with isotretinoin for 5 to 9 months, found no patient who required discontinuation because of liver tests; elevations occurred in a "minority of patients", with peak ALT levels of 40-240 U/L).

Kreiss C, Amin S, Nalesnik MA, Chopra K, Shakil AO. Severe cholestatic hepatitis in a patient taking acitretin. Am J Gastroenterol 2002; 97: 775-7. PubMed PMID: 11922592.

(51 year old man with psoriasis developed jaundice 3 months after starting acitretin [bilirubin ~12 rising to 70 mg/dL, initial ALT ~4500 U/L, Alk P ~550 U/L] and had a prolonged relapsing course despite prednisone therapy; liver biopsy showed intrahepatic cholestasis and fibrosis).

Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. Expert Opin Drug Saf 2004; 3: 119-29. PubMed PMID: 15006718.

(Review of myriad of toxicities of isotretinoin from clinical trials: approximately 15% of patients have mild-to-moderate liver test abnormalities, although frank hepatotoxicity is "a fairly rare event").

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).

Amichai B, Shemer A, Grunwald MH. Low-dose isotretinoin in the treatment of acne vulgaris. J Am Acad Dermatol 2006; 54: 644-6. PubMed PMID: 16546586.

(Among 638 patients with moderate acne treated with isotretinoin, improvement in >90%; 5% had ALT elevations [all less than 2 times ULN]; no mention of jaundice, symptomatic hepatitis or dose modification because of liver test abnormalities).

Pang ML, Murase JE, Koo J. An updated review of acitretin-a systemic retinoid for the treatment of psoriasis. Expert Opin Drug Metab Toxicol. 2008; 4: 953-64. PubMed PMID: 18624682.

(Side effects of acitretin are somewhat dose related, liver enzyme elevations in 25-30% of patients, but usually with high dose therapy, occurring 2 to 8 weeks after starting therapy and transient or responding to dose modification).

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).

Leithead JA, Simpson KJ, MacGilchrist AJ. Fulminant hepatic failure following overdose of the vitamin A metabolite acitretin. Eur J Gastroenterol Hepatol 2009; 21: 230-2. PubMed PMID: 19092674.

(42 year old woman took an 600 mg overdose of acitretin and presented 2 days later with acute liver failure [bilirubin 5.7 mg/dL, ALT 10,226 U/L, Alk P 153 U/L, protime 51 seconds and renal dysfunction]; acetaminophen levels were undetectable and she recovered spontaneously).

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).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(Among 313 cases of drug induced liver injury seen between 1997 and 2008 at a large hospital in Bangalore, India, no cases were attributed to vitamin A or retinoids).

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 Citation (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).

Mas Morey P, Nigorra Caro M, Cladera Serra A, Nicolás Picó J. Possible fulminant toxicity by all-trans-retinoic acid in a patient with acute promyelocytic leukemia. Farm Hosp 2011; 35: 44-5. (33 year old woman with promyelocytic leukemia treated with all-trans-retinoic acid developed acute liver failure within 3 weeks of starting [bilirubin 1.1 rising to 17.4 mg/dL], with progressive pulmonary and renal failure and death 25 days after starting). PubMed PMID: 20605103.

Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int 2011; 31: 595-605. PubMed Citation (Review of the hepatotoxicity of herbals and nutritional supplements including vitamin A, toxic levels being above 50,000 IU daily, but toxic dose is lower in persons with risk factors such as underlying liver disease).

Vieira AS, Beijamini V, Melchiors AC. The effect of isotretinoin on triglycerides and liver aminotransferases. An Bras Dermatol 2012; 87: 382-7. PubMed PMID: 22714752.

(Among 70 patients treated with isoretinoin for 4 to 12 months, mean serum ALT levels increased from 18 to 23 U/L, but no mention of clinically apparent liver injury or discontinuations).

Tripathi SV, Gustafson CJ, Huang KE, Feldman SR. Side effects of common acne treatments. Expert Opin Drug Saf 2013; 12: 39-51. PubMed PMID: 23163336.

(Review of side effects of acne treatments including isoretinoin mentioning that it can cause hepatitis, for which reason monitoring of aminotransferase levels is recommended).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, Presentation and Outcomes in Patients with Drug-Induced Liver Injury in the General Population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, three of which were attributed to isotretinoin [ranking 6th in frequency] all of which were anicteric and only one symptomatic).

Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. JAMA Dermatol 2013; 149: 1392-8. (Among 116 patients with severe acne treated with isotretinoin, ALT levels above 105 U/L arose in only 1 patient). PubMed PMID: 24173086.

Kızılyel O, Metin MS, Elmas ÖF, Çayır Y, Aktaş A. Effects of oral isotretinoin on lipids and liver enzymes in acne patients. Cutis 2014; 94: 234-8. PubMed PMID: 25474452.

(In a retrospective analysis of 320 patients with acne treated with isotretinoin for up to 6 months, average ALT levels increased, but the change was not statistically significant).

Fernández-Crehuet P, Fernández-Crehuet JL, Allam MF, Fernández-Crehuet Navajas R. Hepatotoxicity of isotretinoin in patients with acne and Gilbert's syndrome: a comparative study. BMJ Open 2014; 4: e004441. PubMed PMID: 24650805.

(Among 37 patients with acne treated with isotretinoin for up to 20 weeks, serum bilirubin and ALT levels did not worsen, bilirubin levels actually falling in 11 patients with Gilbert's syndrome).

Lérisson M, Ripault MP, Pageaux GP, Guillot B, Larrey D. Hepatitis after retinoid percutaneous administration. Clin Res Hepatol Gastroenterol 2014; 38: e99-e101. PubMed PMID: 24969684.

(55 year old woman with Darier disease developed anicteric hepatitis 10 months after starting acitretin [bilirubin 0.4 mg/dL, 107 U/L, Alk P 319 U/L] which resolved on stopping, but reappeared 8 months after starting topical acitretin [bilirubin 0.7 mg/dL, ALT 403 U/L, Alk P 203 U/L], resolving 6 months after stopping).

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).

Homma Y, Otani N, Ishimatsu S. A case report of acute vitamin A intoxication due to ocean perch liver ingestion. J Emerg Med 2015; 49: 15-7. PubMed PMID: 25850632.

(27 year old man developed flushing, headache, nausea and joint pains one day after eating 800 g of ocean perch liver, with normal liver enzymes, but high retinol levels and subsequent facial desquamation).

Mengual-Moreno E, Lizarzábal-García M, Ruiz-Soler M, Silva-Suarez N, Andrade-Bellido R, Lucena-González M, Bessone F, et al. [Case reports of drug-induced liver injury in a reference hospital of Zulia state, Venezuela]. Invest Clin 2015; 56: 3-12. Spanish. PubMed PMID: 25920181.

(During a one year period, 13 cases of drug induced liver injury were seen at a single hospital in Venezuela, the implicated agents being acetaminophen [3], ibuprofen [3], isoniazid [2], Herbalife products [2: one fatal], and 1 each of isotretinoin, amoxicillin/clavulanate and methotrexate).

Sauder MB, Cheung L, Beecker J. Acitretin-induced hepatitis: when to monitor cholestatic enzymes. J Cutan Med Surg 2015; 19: 115-20. PubMed PMID: 25775629.

(69 year old woman with bullous lichen sclerosus developed serum enzyme elevations without symptoms or jaundice within 2 weeks of starting acitretin and prednisone [bilirubin normal, peak ALT 328 U/L, Alk P 295 U/L], improving rapidly upon stopping acitretin, later tolerating methotrexate).

Ahmad HM. Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. Dermatol Ther 2015; 28: 151-7. PubMed PMID: 25754162.

(Among 58 patients wtih acne treated with isotretinoin for an average of 22 weeks, ALT levels increased by 21% with once daily and 3% with twice daily administration of the same average dose, but all elevations were transient and less than 100 U/L).

Bugdayci G, Polat M, Oguzman H, Cinpolat HY. Interpretation of biochemical tests Using the reference change Value in monitoring adverse effects of oral isotretinoin in 102 ethnic Turkish patients. Lab Med 2016; 47: 213-9. PubMed PMID: 27346869.

(Among 102 Turkish patients with acne, ages 15 to 37 years, treated with oral isotretinoin for 24 weeks, mean ALT and AST values did not change, but instances of "Reference Change Values" were more frequent than in controls).

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 PMID: 27131947.

(16 year old girl with acne developed serum enzyme elevations 3 months after starting isotretinoin [ALT 1196 U/L, Alk P 114, ANA 1:180] and improved with stopping isotretinin and starting corticosteroid therapy).

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