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Fulvestrant

Updated: February 6, 2018.

OVERVIEW

Introduction

Fulvestrant is a steroidal antiestrogen that is used in the treatment of hormone-receptor positive metastatic breast cancer. Fulvestrant therapy can be associated with serum enzyme elevations, but has yet to be linked to instances of clinically apparent acute liver injury in the published literature.

Background

Fulvestrant (ful ves' trant) is a steroidal antiestrogen that is potent and direct antagonist or "down regulator" of the estrogen receptor. Fulvestrant is a synthetic derivative of estradiol and binds to the estrogen receptor with 100 times more potency than tamoxifen. It not only blocks the effects of estrogen, but also alters the structure of the estrogen receptor and further decreases the intracellular effects of estrogen. Unlike tamoxifen, fulvestrant is a pure antiestrogen and has no estrogen receptor agonist activity. Fulvestrant has been found to be as effective as tamoxifen as a first line agent to treat metastatic breast cancer, and is similar in efficacy to the aromatase inhibitors in women with progressive disease despite tamoxifen therapy. Fulvestrant was approved for use in the United States in 2002. Current indications are for treatment of postmenopausal women with hormone-receptor positive metastatic breast cancer who have had disease progression despite antiestrogen therapy. Fulvestrant is available as a liquid solution in 5 mL vials of 250 mg for intramuscular injection under the brand name Faslodex. The usual dose for treating breast cancer is 500 mg given in two intramuscular injections in the buttocks (slowly, over 1-2 minutes) on days 1, 15 and 29, and then monthly thereafter. Common side effects include injection site pain and reactions, nausea, anorexia, fatigue, headache, backache, muscle pains, host flashes, cough, dyspnea and constipation. Rare, but potentially severe side effects include hypersensitivity reactions.

Hepatotoxicity

Fulvestrant therapy is said to be associated with serum enzyme elevations in up to 15% of patients, but the elevations are generally asymptomatic, transient and mild, rarely requiring dose adjustment or discontinuation. ALT elevations above 5 times the upper limit of normal occurred in only 1% to 2% of patients. However, specifics on the timing and course of serum enzyme elevations during fulvestrant therapy have not been described. In addition, no cases of clinically apparent liver injury with jaundice were reported in the prelicensure controlled trials of fulvestrant and none have been published since its approval in the United States and more wide-scale use. Nevertheless, the product label for fulvestrant mentions that "hepatitis and liver failure have been reported infrequently (<1%)". Unlike tamoxifen, fulvestrant has not been linked to steatosis or nonalcoholic fatty liver, nor has it been found to cause the bland cholestasis that can occur with oral contraceptives or high dose estrogen therapy.

Likelihood score: E* (unproven but suspected cause of clinically apprent liver injury).

Mechanism of Injury

Fulvestrant is extensively metabolized in the liver, largely via the cytochrome P450 enzyme CYP 3A4, but has not been found to have significant drug-drug interactions. Nevertheless, hepatotoxicity might be caused by a toxic or immunogenic metabolic product of fulvestrant.

Outcome and Management

While fulvestrant has been reported to cause serum enzyme elevations during therapy, it has not been convincing linked to cases of clinically apparent liver injury, acute liver failure, chronic hepatitis, fatty liver or vanishing bile duct syndrome. There is no reason to suspect that there is cross sensitivity to liver injury between fulvestrant and other antiestrogens such as tamoxifen and the aromatase inhibitors.

Drug Class: Antineoplastic Agents, Antiestrogens

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Fulvestrant – Generic, Faslode®

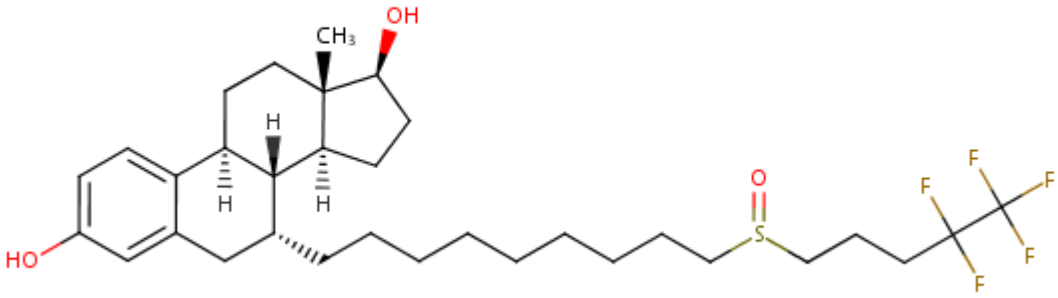
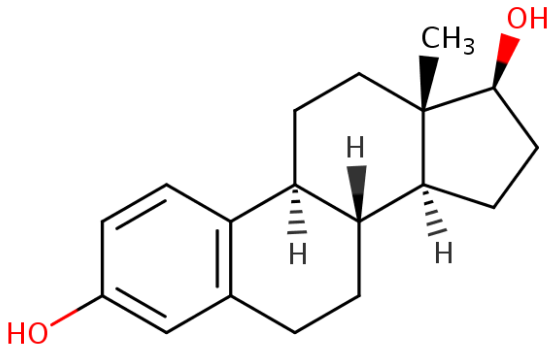
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Fulvestrant	129453-61-8	C32-H47-F5-O3-S	
Estradiol(17-β)	50-28-2	C18-H24-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 06 February 2018

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 699.

(Expert review of hepatotoxicity published in 1999; fulvestrant is not discussed).

Chitturi S, Farrell GC. Estrogen receptor antagonists. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 610-2.

(Review of hepatotoxicity of estrogens and antiestrogens discusses tamoxifen but not fulvestrant).

Moy B, Lee RJ, Smith M. Anti-estrogen therapy. Natural products in cancer chemotherapy. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1756-9.

(Textbook of pharmacology and therapeutics).

Fulvestrant (Faslodex) for advanced breast cancer. Med Lett Drugs Ther 2002; 44: 65-6. PubMed PMID: 12138378.

(Concise summary of the mechanisms of action, pharmacokinetics, efficacy, safety and costs of fulvestrant for advanced breast cancer; no mention of ALT elevations or hepatotoxicity).

Bross PF, Cohen MH, Williams GA, Pazdur R. FDA drug approval summaries: fulvestrant. Oncologist 2002; 7: 477-80. PubMed PMID: 12490735.

(Review of the evidence for safety and efficacy of fulvestrant which was the basis for the FDA approval; in 2 controlled trials comparing fulvestrant to anastrozole for 2 years, response rates were similar and common side effects of fulvestrant were injection site pain, hot flashes, fatigue, headache, nausea, diarrhea and rash; no mention of ALT elevations or clinically apparent liver injury).

Robertson JF, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Macpherson E, Lindemann J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol 2009; 27: 4530-5. PubMed PMID: 19704066.

(Among 205 women with estrogen-receptor positive advanced breast cancer treated with fulvestrant [500 mg doses] or anastrozole, tolerability and drop-out rates were similar during the first 6 months; no mention of ALT elevations or hepatotoxicity).

Flemming J, Madarnas Y, Franek JA. Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: a systematic review. Breast Cancer Res Treat 2009; 115: 255-68. PubMed PMID: 18683044.

(Systematic review of 4 controlled trials of fulvestrant versus anastrozole or exemestane, found similar rates of efficacy and tolerance; no mention of ALT elevations or hepatotoxicity).

Pritchard KI, Rolski J, Papai Z, Mauriac L, Cardoso F, Chang J, Panasci L, et al. Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). Breast Cancer Res Treat 2010; 123: 453-61. PubMed PMID: 20632084.

(Controlled trial of 3 doses of fulvestrant [250 to 500 mg] in 94 women with metastatic breast cancer after failure of antiestrogen therapy found similar rates of efficacy and adverse events; no mention of ALT elevations or hepatotoxicity).

Howell A, Bergh J. Insights into the place of fulvestrant for the treatment of advanced endocrine responsive breast cancer. J Clin Oncol 2010; 28: 4548-50. PubMed PMID: 20855842.

(Editorial on the pharmacokinetics of fulvestrant describing the evidence that a higher dose [500 mg] is slightly more effective and just as well tolerated as the initially approved dose [250 mg] in prolonging progression-free survival).

Robertson JF, Lindemann JP, Llombart-Cussac A, Rolski J, Feltl D, Dewar J, Emerson L, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat 2012; 136: 503-11. PubMed PMID: 23065000.

(Among 205 women with estrogen receptor positive advanced breast cancer treated with fulvestrant [500 mg] or anastrozole, time to progression was longer with fulvestrant and no new safety concerns were identified; ALT elevations were not mentioned and there were no liver related serious adverse events).

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, but none of the 96 were attributed to fulvestrant or any other antiestrogen).

Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, Verhoeven D, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst 2014; 106: djt337. PubMed PMID: 24317176.

(Among 736 women with metastatic estrogen-receptor positive breast cancer treated with either 250 or 500 mg of fulvestrant monthly, there were no important differences in adverse reactions and no serious hepatic adverse events).

Ellis AJ, Hendrick VM, Williams R, Komm BS. Selective estrogen receptor modulators in clinical practice: a safety overview. Expert Opin Drug Saf 2015: 14: 921-34. PubMed PMID: 25936229.

(Overview of the safety of estrogen receptor modulations used to treat or prevent breast cancer and for osteoporosis includes discussion of tamoxifen, raloxifene and fulvestrant and focuses upon cardiovascular and cancer related safety issues, with no mention of ALT elevations or hepatotoxicity).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 4 were attributed to tamoxifen, 2 to exemestane and 1 to letrozole, but none to fulvestrant).

Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, Hewson N, Rukazenkov Y, Robertson JF. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II FIRST study. J Clin Oncol 2015; 33: 3781-7. PubMed PMID: 26371134.

(Among 205 women with advanced breast cancer treated with fulvestrant or anastrozole, overall median survival was 54 vs 48 months and "no new safety issues were observed"; no mention of ALT elevations or hepatotoxicity).

Zhang Q, Shao Z, Shen K, Li L, Feng J, Tong Z, Gu K, et al. Fulvestrant 500 mg vs 250 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer: a randomized, double-blind registrational trial in China. Oncotarget 2016; 7: 57301-9. PubMed PMID: 27359058.

(Among 221 Chinese postmenopausal women with advanced breast cancer treated with fulvestrant [250 vs 500 mg daily], median progression free survival was higher with the higher dose [8 vs 4 months] while overall side effect rates were similar, and there were no discontinuations for severe adverse events or mention of liver related side effects).

Lerebours F, Rivera S, Mouret-Reynier MA, Alran S, Venat-Bouvet L, Kerbrat P, Salmon R, et al. Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). Cancer 2016; 122: 3032-40. PubMed PMID: 27315583.

(Among 116 women with operative breast cancer given adjuvant therapy with anastrozole or fulvestrant, both therapies were well tolerated with no serious adverse events or mention of ALT elevations or liver related adverse events).

Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, Shparyk Y, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet 2016; 388 (10063): 2997-3005. PubMed PMID: 27908454.

(Among 462 women with advanced breast cancer treated with fulvestrant vs anastrozole, median progression free survival was higher with fulvestrant [16.6 vs 13.8 months], while overall side effect rates were similar, ALT elevations arising in 7% vs 3%, but there were no liver related serious adverse events).

Baselga J, Im SA, Iwata H, Cortés J, De Laurentiis M, Jiang Z, Arteaga CL, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18: 904-16. PubMed PMID: 28576675.

(Among 1147 postmenopausal women with advanced breast cancer treated with fulvestrant with or without buparlisib [pan PI3 inhibitor], prgression free survival was slightly higher in the buparlisib group, although adverse events were also more common).

Di Leo A, Johnston S, Lee KS, Ciruelos E, Lønning PE, Janni W, O'Regan R, et al. Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2018; 19: 87-100. PubMed PMID: 29223745.

(Among 432 women with refractory, advanced breast cancer treated with fulvestrant with or without buparlisib, progression free survival was similar in both groups, while side effects were move frequent with the combination, ALT elevations arising in 39% vs 7% and rising above 5 times ULN in 22% vs 3%).