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Triptorelin

Updated: March 22, 2018.

OVERVIEW

Introduction

Triptorelin is a gonadotropin releasing hormone (GnRH) agonist that is a potent inhibitor of the synthesis of testosterone (in men) and estrogen (in women) and is used to treat advanced prostate cancer. Triptorelin is associated with a low rate of transient serum enzyme elevations during therapy, but has not been linked convincingly to cases of clinically apparent acute liver injury.

Background

Triptorelin (trip" toe rel' in) is a decapeptide analogue of gonadotropin releasing hormone (GnRH) that acts on the pituitary to cause the synthesis and release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), two gonadotropins that act on the male testes to stimulate the production of testosterone and on the female ovaries to induce synthesis of estrogen. Triptorelin and other GnRH agonists cause an initial surge of gonadotropin release, but then lead to down-regulation of their synthesis and secretion which results in a decline in testosterone and estrogen production. Triptorelin, alone or in combination with other antiandrogens, has been found to be palliative in advanced prostate cancer and as effective as surgical castration. Triptorelin was approved for use in the United States for prostate cancer in 2000 and is still widely used, being considered a first line treatment of this hormone responsive malignancy. Triptorelin is available generically and under the brand name Trelstar in an injectable suspension for intramuscular depot administration every 4 weeks (3.75 mg), 12 weeks (11.25 mg) or 24 weeks (22.5 mg). Triptorelin and the other GnRH analogues cause a profound hypogonadism ("chemical castration") and its common side effects are typical of androgen deprivation, including hot flashes, loss of libido, erectile dysfunction, depression, nausea, diarrhea, weight gain and fluid retention. Rare, but potentially severe adverse events can include immediate hypersensitivity reactions, pituitary apoplexy and, with long term use, weight gain, metabolic changes, diabetes and osteoporosis.

Hepatotoxicity

Long term triptorelin is associated with serum enzyme elevations in 2% to 5% of patients, although the elevations are rarely above three times the upper limit of normal (<1%). The enzyme elevations are usually mild, asymptomatic and resolve even without dose modification or drug discontinuation. Triptorelin has not been linked convincingly to cases of acute, clinically apparent liver injury with jaundice.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the minor serum enzyme elevations that can occur during triptorelin therapy is unknown. Triptorelin is a decapeptide similar to GnRH and is metabolized locally in tissue and not by the hepatic cytochrome P450 system. Some serum enzyme elevations may be caused by nonalcoholic fatty liver arising because of weight gain or metabolic changes caused by the androgen deprivation state induced by the GnRH agonist.

Outcome and Management

The serum enzyme elevations during triptorelin therapy rarely require dose modification or drug discontinuation and should instead lead to investigation of other possible causes of liver injury. There is no evidence to indicate that there is cross sensitivity to liver injury among the various GnRH analogues.

Drug Class: Antineoplastic Agents, GnRH Analogues

Other Drugs in the Subclass, GnRH Analogues: Degarelix, Goserelin, Histrelin, Leuprolide

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Triptorelin – Generic, Trelstar®

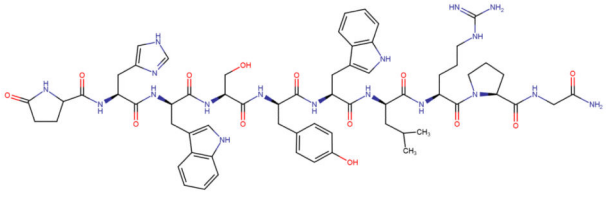
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Triptorelin	57773-63-4	C64-H82-N18-O13	

ANNOTATED BIBLIOGRAPHY

References updated: 22 March 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; the GnRH analogues such as triptorelin are 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 hormonal products; does not discuss the GnRH agonists such as triptorelin).

Moy B, Lee RJ, Smith M. Gonadotrophin-releasing hormone agonists and antagonists. Natural products in cancer chemotherapy: hormones and related agents. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1764.

(Textbook of pharmacology and therapeutics).

Triptorelin pamoate (Trelstar). Med Lett Drugs Ther 2002; 44 (1132): 51-2. PubMed PMID: 12058149.

(Concise review of the mechanism of action, efficacy, safety and costs of triptorelin for prostate cancer shortly after its approval in the US; mentions that adverse effects are similar to those of goserelin; does not mention ALT elevations or hepatotoxicity).

Heyns CF, Simonin MP, Grosgurin P, Schall R, Porchet HC; South African Triptorelin Study Group. Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer. BJU Int 2003; 92: 226-31. PubMed PMID: 12887472.

(Among 284 men with prostate cancer treated with triptorelin or leuprolide in 9 monthly injections, both beneficial and adverse effects were similar and "there were no substantial changes in laboratory data"; ALT levels were not specifically mentioned).

Carel JC, Blumberg J, Seymour C, Adamsbaum C, Lahlou N; Triptorelin 3-month CPP Study Group. Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty. Eur J Endocrinol 2006; 154: 119-24. PubMed PMID: 16382000.

(Among 64 children [54 girls] with central precocious puberty treated with triptorelin acetate depot injections every 3 months for 1 year, pubertal regression occurred in most subjects and adverse events were generally mild and self-limited; no mention of ALT elevations or hepatotoxicity).

Lundström EA, Rencken RK, van Wyk JH, Coetzee LJ, Bahlmann JC, Reif S, Strasheim EA, et al. Triptorelin 6-month formulation in the management of patients with locally advanced and metastatic prostate cancer: an open-label, non-comparative, multicentre, phase III study. Clin Drug Investig 2009; 29: 757-65. PubMed PMID: 19888782.

(Among 120 patients given triptorelin in 6 month formulation [22.5 mg] for one year, the most common side effects were hot flashes [72%], erectile dysfunction [10%] and injection site reactions [7%], and one patient had a rise in ALT levels [peak=60 U/L] on day 337).

Rabaglio M, Ruepp B; Soft/Text/Perche Steering Committee. Death due to liver failure during endocrine therapy for premenopausal breast cancer. Acta Oncol 2010; 49: 874-6. PubMed PMID: 20482225.

(Among 4500 women enrolled in an international trial of endocrine therapy of premenopausal breast cancer comparing tamoxifen and exemestane combined with ovarian suppression often with triptorelin, 2 developed liver failure: 50 year old on endocrine therapy for two years developed suspected acute alcoholic hepatitis and died 1 month later [bilirubin 23.2 mg/dL, ALT 182 U/L, AST 294 U/L, GGT 2623 U/L, Alk P 382 U/L]; 36 year old woman on endocrine therapy including tamoxifen for 3 years developed nonspecific symptoms and hepatomegaly and died suddenly, autopsy showing cirrhosis with steatosis, possibly due to or exacerbated by tamoxifen; in neither case could triptorelin be convincingly implicated).

Crawford ED, Phillips JM. Six-month gonadotropin releasing hormone (GnRH) agonist depots provide efficacy, safety, convenience, and comfort. Cancer Manag Res 2011; 3: 201-9. PubMed PMID: 21847353.

(Review of results on two GnRH agonist depot formulations for advanced prostate cancer that allow for every 6 month administration [leuprolide and triptorelin], both of which provide sustained testosterone suppression and have adverse side effects similar to other GnRH agonist formulations; mentions a single episode of minor asymptomatic ALT [60 U/L] and AST [65 U/L] elevations in a patient receiving triptorelin [Ludström 2009]).

Del Mastro L, Boni L, Michelotti A, Gamucci T, Olmeo N, Gori S, Giordano M, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause inpremenopausal women with breast cancer: a randomized trial. JAMA 2011; 306: 269-76. PubMed PMID: 21771987.

(Among 181 premenopausal women with breast cancer treated with chemotherapy alone or combined with triptorelin [for 6 months], early onset of menopause was less common with triptorelin therapy [9% vs 26%] and adverse events were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Boccon-Gibod L, van der Meulen E, Persson BE. An update on the use of gonadotropin-releasing hormone antagonists in prostate cancer. Ther Adv Urol 2011; 3: 127-40. PubMed PMID: 21904569.

(GnRH antagonists such as degarelix have similar efficacy to GnRH agonists in therapy of prostate cancer, but have a more rapid onset of action and do not cause the initial testosterone surge that occurs with the agonists, which can be particularly troublesome in patients with a large tumor burden).

Van Poppel H, Klotz L. Gonadotropin-releasing hormone: an update review of the antagonists versus agonists. Int J Urol 2012; 19: 594-601. PubMed PMID: 22416801.

(Review of androgen deprivation therapy for prostate cancer using GnRH agonists and antagonists stressing the more rapid onset of action and similar if not better safety profile of GnRH antagonists).

Walker LM, Tran S, Robinson JW. Luteinizing hormone--releasing hormone agonists: a quick reference for prevalence rates of potential adverse effects. Clin Genitourin Cancer 2013; 11: 375-84. PubMed PMID: 23891497.

(Systematic review of adverse event profile of long term use of GnRH agonists which mostly relate to hypogonadism: hot flashes, gynecomastia, genital shrinkage, hair loss, osteoporosis, mild anemia, hyperglycemia, increased weight, loss of skeletal muscle mass, emotional lability, depression, loss of sexual desire and erectile dysfunction; no mention of ALT elevations or hepatotoxicity).

Ploussard G, Mongiat-Artus P. Triptorelin in the management of prostate cancer. Future Oncol 2013; 9: 93-102. PubMed PMID: 23252566.

(Review of the efficacy and safety of triptorelin as therapy of prostate cancer focusing upon 1 vs 3 vs 6 monthly formulations; no mention of ALT elevations or hepatotoxicity).

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 were attributed to triptorelin or any of the GnRH analogues).

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, none were attributed to triptorelin or any of the GnRH analogues).

Lambertini M, Boni L, Michelotti A, Gamucci T, Scotto T, Gori S, Giordano M, et al; GIM Study Group. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function,

pregnancies, and disease-Free survival: a randomized clinical trial. JAMA 2015; 314: 2632-40. PubMed PMID: 26720025.

(Among 281 premenopausal women with breast cancer treated with chemotherapy with or without triptorelin [Del Mastro 2011], long term disease-free survival rates were similar while rates of menstrual resumption were slightly higher with triptorelin; no mention of adverse events, ALT elevations or hepatotoxicity).

Zenaty D, Blumberg J, Liyanage N, Jacqz-Aigrain E, Lahlou N, Carel JC; Co-Investigators. A 6-month trial of the efficacy and safety of triptorelin pamoate (11.25 mg) every 3 months in children with precocious puberty: a retrospective comparison with triptorelin acetate. Horm Res Paediatr 2016; 86: 188-95. PubMed PMID: 27603324.

(Among 37 children with precocious puberty treated with triptorelin pamoate depot injections every 3 months, pubertal regression occurred in most and adverse events were generally mild and self-limited; no mention of ALT elevations or hepatotoxicity).

Schagen SE, Cohen-Kettenis PT, Delemarre-van de Waal HA, Hannema SE. Efficacy and Safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. J Sex Med 2016; 13: 1125-32. PubMed PMID: 27318023.

(Among 49 male-to-female and 67 female-to-male gender dysphoric adolescents treated with triptorelin for at least 6 months, ALT and AST elevations were present in 5% to 10% of subjects at baseline and levels did not change during treatment, however, growth velocity slowed and lean body mass decreased while fat percentage increased).

Bolton EM, Lynch TH. Are all gonadotropin-releasing hormone agonists equivalent for the treatment of prostate cancer? A systematic review. BJU Int 2018;122 (3): 371-83. PubMed PMID: 29438592.

(Systematic review of literature on relative efficacy and safety of different GnRH agonists, indicates that there is little evidence of superiority of any of the four, largely because of lack of adequately powered, controlled studies comparing them).