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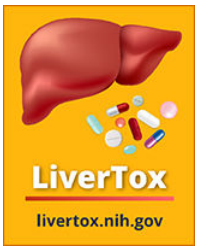

Gonadotropin Releasing Hormone (GnRH) Analogues

Updated: March 20, 2018.

OVERVIEW

Introduction

The gonadotropin releasing hormone (GnRH) agonists and antagonists are short peptide analogues of GnRH that cause a profound inhibition of estrogen and androgen synthesis and are used predominantly as androgen deprivation therapy of advanced prostate cancer. Some of these agents are also used to treat benign conditions responsive to hormonal inhibition such as endometriosis, uterine fibroids, precocious puberty and infertility. Leuprolide, goserelin, triptorelin and histrelin are considered GnRH agonists, whereas degarelix acts predominantly as an antagonist. Several of the GnRH analogues have been reported to be associated with transient serum enzyme elevations during therapy, but none have been convincingly implicated in causing clinically significant liver injury with jaundice.

Background

Gonadotropin releasing hormone is a decapeptide that is produced in the hypothalamus and acts upon GnRH receptors on the surface of gonadotropin cells in the pituitary gland, stimulating the release of luteinizing hormone (LH) and follicular stimulating hormone (FSH) which, in turn, stimulate the production and release of testosterone by the male testes and estrogen by the female ovaries and placenta. GnRH is typically produced in a pulsatile manner, and its synthesis is regulated by circulating levels of testosterone in men and estrogens in women. Infusions of GnRH agonists produce an initial transient increase in sex hormones, but with continued non-pulsatile stimulation, LH and FSH synthesis are inhibited and estrogen and testosterone levels decline. GnRH analogues have been found to be much more potent and sustained in action that the native decapeptide and have been used extensively in modulation of sex hormone synthesis. The GnRH analogue degarelix acts in a somewhat different manner in that it is an antagonist of the gonadotropin receptors in the pituitary and inhibit LH and FSH synthesis and release directly, and without an initial surge that is typical of the GnRH agonists. The ultimate effects and efficacy of the GnRH agonists and antagonist are similar, the difference being a more rapid onset and the lack of an initial surge in sex hormone release with the pure antagonist.

The commercial names and year of approval in the United States of the currently available forms of GnRH agonists and antagonists are: leuprolide, also called leuprorelin (Lupron: 1985), goserelin (Zoladex: 1989), histrelin (Supprelin, Vantas: 1991 and 2004), triptorelin (Trelstar: 2000), and degarelix (Firmagon: 2008). Many of these agents are now available in generic forms as well. Long acting forms that allow for administration at 1, 3, 6 and even 12-month intervals are available for some GnRH analogues. The GnRH analogues all require parenteral (subcutaneous or intramuscular) administration and are used largely as androgen deprivation therapy for advanced prostate cancer. They are used off-label for precocious puberty, gender dysphoria and infertility.

Common side effects of the GnRH agonists and antagonists include symptoms of hypogonadism such as hot flashes, gynecomastia, fatigue, weight gain, fluid retention, erectile dysfunction and decreased libido. Long term therapy can result in metabolic abnormalities, weight gain, worsening of diabetes and osteoporosis. Rare, but potentially serious adverse events include transient worsening of prostate cancer due to surge in testosterone with initial injection of GnRH agonists and pituitary apoplexy in patients with pituitary adenoma. Single instances of clinically apparent liver injury have been reported with some GnRH agonists (histrelin, goserelin), but the reports were not very convincing. There is no evidence to indicate that there is cross sensitivity to liver injury among the various GnRH analogues despite their similarity in structure.

Five GnRH analogues are discussed separately with specific references to their safety and hepatotoxicity at the end of each section. General references are given below.

Drug Class: Antineoplastic Agents; Obstetrical and Gynecological Agents

GnRH Analogues: Degarelix, Goserelin, Histrelin, Leuprolide, Triptorelin

ANNOTATED BIBLIOGRAPHY

References updated: 20 March 2018

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 731-4.

(Expert review of hepatotoxicity published in 1999, before the availability of GnRH analogues).

DeLeve LD. Hormones. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 699.

(Review of hepatotoxicity published in 2007; the GnRH analogues are not discussed).

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).

Maillefert JF, Sibilia J, Kuntz JL, Tavernier C. Gonadotrophin-releasing hormone agonists induce osteoporosis. Br J Rheumatol 1994; 33: 1199-200. PubMed PMID: 8000764.

(58 and 69 year old men with prostate cancer were treated with leuprolide for 3 years and triptorelin for 9 months when they presented with back pain and vertebral fractures, which were not present on pretreatment imaging).

Hands KE, Alvarez A, Bruder JM. Gonadotropin-releasing hormone agonist-induced pituitary apoplexy in treatment of prostate cancer: case report and review of literature. Endocr Pract 2007; 13: 642-6. PubMed PMID: 17954421.

(Review of 7 cases of pituitary apoplexy occurring after initiation of GnRH agonist therapy for prostate cancer).

Guerra Y, Lacuesta E, Marquez F, Raksin PB, Utset M, Fogelfeld L. Apoplexy in non functioning pituitary adenoma after one dose of leuprolide as treatment for prostate cancer. Pituitary 2010; 13: 54-9. PubMed PMID: 19842040.

(60 year old man with prostate cancer developed headaches and neurologic symptoms within 24 hours of a first injection of leuprolide, and subsequent evaluation revealed a previously unsuspected nonfunctioning pituitary adenoma).

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).

Duburque C, Bonnal JL, Gosset P, Lucidarme D. [Could gosereline acetate induce autoimmune-like hepatitis?]. Prog Urol 2012; 22 (10): 610-2. French. PubMed PMID: 22920341.

(59 year old man with prostate cancer and heavy alcohol intake [80 g daily] developed jaundice 6 weeks after stopping bicalutamide and 10 days after a 2nd every-12-week injection of goserelin [bilirubin 21.3 mg/dL, ALT 50 times ULN, Alk P 2 times ULN, ANA 1:640, MCV 105], resolving 4 months after onset).

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).

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 a GnRH analogue).

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 a GnRH analogue)

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).