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PCa Commentary
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LUPRON vs FIRMAGON: Is The Debate About Superiority Over? Just the Facts, Please, … but with the December FDA approval of Relugolix the debate may now be moot.

A great deal has been written about the comparison between Lupron (leuprolide) and Firmagon (degarelix). Lupron as been the mainstay of treatment of relapsed and metastatic prostate cancer since its introduction in the early 1990's. Firmagon (degarelix) was FDA approved in 2008.

The prevailing consensus is that degarelix is the superior drug.

This conclusion is not unchallenged. The differences in opinion, however, may result from the lack of randomized preclinical studies specifically addressing this comparison, but one currently is in progress. Many clinical trials exclude candidates who have significant cardiovascular morbidity making reviews based on "real-life" observational studies more informative.

There is no dispute, however, with the choice of degarelix as initial treatment of men with metastatic disease located in the spine proximal to the spinal cord. The early testosterone "flare" associated with Lupron has the potential of promoting cancer growth and paralysis due to spinal cord compression. Degarelix produces no "flare".

This Commentary will discuss the difference in cardiotoxicity between Lupron and degarelix focusing on major cardiovascular adverse events, e.g., heart attacks, strokes, and other cardiovascular diseases (CVD). As background, 20-30% of prostate cancer patients have pre-existing cardiac conditions. About 30% of men who have survived their prostate cancer for 10 years will die from cardiovascular disease. The risk factors that predispose to CVD frequently occur in older men: hypertension, elevated cholesterol and triglycerides, and smoking. The high prevalence of the risk factors underscores the importance of degarelix's lesser cardiotoxicity.

A Bit of Biology:

Lupron (the 'agonist') stimulates receptors in the pituitary gland to release luteinizing hormone (LH) which in turn stimulates the Leydig cells of the testicles to secrete testosterone (T). After an initial several days of strong stimulation (the cause of the T 'surge') the receptors become exhausted, diminish LH secretion, and serum T drops to below 50 ng/ml in a week or so. Contrariwise, degarelix (the 'antagonist') blocks the receptor, causing an abrupt fall in T over 2-3 days to the even lower levels of < 30 ng/ml, the currently recommended target.

Lupron and degarelix both promote the secretion of an additional pituitary hormone, FSH (Follicle Stimulating Hormone). The relevance of FSH to prostate cancer is not fully understood. Degarelix causes an immediate and sustained reduction of FSH to <90% of baseline. Contrariwise, Lupron affects an initial FSH surge but results long-term in a level 10-20% below baseline. Malignant prostate cells express FSH receptors. Research suggests that FSH promotes prostate cancer aggressiveness. FSH may also contribute to inflammation within plaques causing rupture. (Crawford and Schally, *Canadian Journal of Urology,* April 2020).

Cardiovascular Risk Due to Suppressed Testosterone: Three studies; similar findings.

** A Report of "Real-Life Experience from UK General Practice" was presented in the November 16, 2020, issue of UroToday by Patrick Davey and Michael Kirby: "Cardiovascular Risk Profiles of GnRH Agonists and Antagonists." In their study of 9,081 patients "the relative risk of experiencing *any* cardiac events was lower with degarelix than all other [predominantly Lupron and Goserelin] GnRH agonists," i.e., 6.9% vs 17.7%

** Albertsen, Klotz *et al., (Eur Urol,* 2014) in "Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and antagonist" reported a study of 2328 men with prostate cancer that excluded men with risk factors for CVD. Over the course of the one year study comparing Lupron and degarelix, men with *pre-existing* cardiovascular disease treated with degarelix showed a 54% relative risk reduction of myocardial infarction, stroke and other ischemic heart disease.

** Margel *et al., J. Urol.* 2019, presented a small (n=80) one year study analyzing for new CV events in 80 patients with advanced cancer with pre-existing CV disease. Major cardiovascular and cerebrovascular events occurred in 20% receiving agonists vs 3% on the antagonist.

Important take-away points:

Notable in the latter two studies is the extent of CV morbidity manifested *within one year.* This short period argues for an early acting cardiotoxic mechanism. A plausible, but unvalidated, theory posits that depleted T leads to a cascade of events that destabilizes and causes rupture of existing atherosclerotic plaques. Also posited was that resident T-cells within the plaques secrete interferon creating an inflammatory environment which might increase the risk of plaque rupture.

A consistent recommendation from these studies emphasizes the importance that all men who are embarking on androgen deprivation have a careful assessment for prior CV disease and risk factors. The need for informed CV assessment has spawned a new subspecialty, CardioOncology.

Relugolix (Orgovyx) - is a game changer likely to significantly alter the management of recurrent and metastatic prostate cancer and replace *both* Lupron and Firmagon.

The HERO trial is a 930 man phase 3 randomized international study comparing the new agent, relugolix (120 mg orally once daily after a loading dose of 360 mg) to Lupron (22.5 mg IM every 3 weeks) in men with advanced prostate cancer: "Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer." (Shore *et al., NEJM.* June, 2020). The duration of the study was 48 weeks. The end points were the percentage of patients with castrate T levels (<50 ng/dL) at day 4 and the extent of T recovery 90 days after treatment discontinuation.

Executive summary: *All comparisons favored relugolix over leuprolide.*

* At day 4 relugolix achieved castrate T level in 56.0% of men compared to Lupron, 0%. At day 4 the T level was 38 ng/dL for relugolix. Lupron produced a 'surge" to 625 ng/mL day 4 then dropped to castrate level by day 6. The mean pre-treatment T level in the study group was ~ 425 ng/mL

* At day 15 a testosterone level of <20 ng/mL was seen in 78.4% with relugolix vs 1.0%, Lupron.

* Relugolix maintained castrate T levels (<50 ng/mL) in men through 48 weeks in 96.7% of men compared to Lupron, 88.8%.

* At 90 days following the end of treatment the T level was 288.4 ng/mL for relugolix therapy compared to 58.6 ng/mL for Lupron treatment.

* FSH suppression was greater with relugolix than with leuprolide at all available time points.

* Major cardiovascular events were seen in 2.9%, relugolix, compared to 6.2%, Lupron, representing a 54% reduction of cardiovascular event risk.

The rapid onset of T suppression and short recovery period make relugolix particularly suited for use in short periods of T suppression associated with radiation therapy and management with intermittent hormone suppression.

[Myovant, the maker of relugolix, has launched a Orgovyx Patient Support Program to help handle insurance plans and offers a free trial of up to 2 months for uninsured patients. Call 1-833-674-6899 for information]

BOTTOM LINE:

The recently FDA approved oral relugolix is likely to replace both Lupron and degarelix in the management recurrent and metastatic prostate cancer.

Your comments and requests for information on a specific topic are welcome.
Please e-mail Dr. Weber at ecweber@nwlink.com.

Please also visit the website https://prostatecancerfree.org/prostate-cancer-news for a selection of past issues of the PCa Commentary covering a variety of topics.

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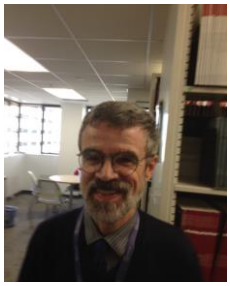

Mike Scully, Librarian

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