Degarelix in the Treatment of Prostate Cancer

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Abstract: Manipulation of the hypothalamic-pituitary-gonadal axis via androgen deprivation therapy has been in use since the 1940's for the treatment of advanced prostate cancer. Androgen deprivation may be achieved via surgical castration or pharmacological castration. Pharmacological castration is preferred by patients due to its decreased psychological impact on body image and potential reversibility. Gonadotropin releasing hormone (GnRH) agonists have been a mainstay in androgen suppression. Recently degarelix, a GnRH antagonist, has been proven to be as effective and not inferior to GnRH analogues, such as leuprolide, in a phase III trial. Degarelix was found to have no initial testosterone surge, reach castrate levels of testosterone by day three, have no testosterone microsurges, have the ability to keep follicle stimulating hormone suppressed and have lower histaminogenic potency compared to its predecessor abarelix. A review of the pharmacokinetics, clinical trial findings, safety and ongoing debates as to the best application of degarelix is presented.

Keywords: degarelix, prostate neoplasm, hormone therapy, gonadotropin-releasing hormone receptor blocker

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Introduction

The recognition that prostate cancer (PCa) is hormonally dependent came about in 1941 with Charles Huggins and Clarence Hodges' report on significant therapeutic responses in patients with metastatic PCa who underwent androgen deprivation.[1] Since that time, androgen deprivation therapy (ADT) remains the first line therapy of advance metastatic PCa. The 2010 National Comprehensive Cancer Network (NCCN), the 2007 American Society of Clinical Oncology (ASCO), and the 2007 European Association of Urology (EUA) guidelines recommend ADT as first line therapy in men with locally advanced and metastatic disease.[24] ADT application has also been studied as primary therapy for localized PCa,[5,6] neoadjuvant therapy prior to radical prostatectomy,[7] adjuvant therapy with external beam radiation,[8,9] and as therapy for biochemical failure after local treatment.[10] Androgen blockade is achieved by either surgical castration (bilateral orchiectomy) or pharmacological castration (anti-androgens, estrogen, gonadotropin-releasing hormone (GnRH) analogues, and GnRH antagonists). The irreversible nature and negative impact on body image has decreased the frequency of surgical castration and has shifted preferences by men with advance PCa for ADT to be achieved with pharmacological castration, a reversible option. GnRH analogues (i.e. leuprolide, goserelin, and triptorelin) are the most frequently used agents for ADT. They act on the hypothalamic-pituitary-gonadal axis by overstimulation of the GnRH receptors. This leads to a desensitization of the pituitary-gonadal axis, ultimately resulting in depressed levels of leuteinising hormone (LH) with a subsequent drop in testosterone to castrate levels in approximately 28 days.[11] An initial testosterone surge is present within 48 hours of administration and peaks at 7 to 10 days. This hormonal surge may exacerbate local symptoms (i.e. retention, bone pain) or cause paraplegia due to spinal cord compression or fractures in patients with advanced symptomatic PCa.[12] In order to help prevent this, anti-androgens (i.e. bicalutamide, flutamide, nilutamide) are given in combination with GnRH analogues in patients at risk.[13] GnRH antagonists such as degarelix and abarelix, offer a form of ADT that avoids the initial testosterone surge and drops testosterone levels rapidly. Although abarelix received approval from the Food and Drug Administration (FDA) for the treatment of men with metastatic PCa, its use was restricted to patients who had no other options for therapy due to its risk of potentially life-threatening allergic reaction.[14] Degarelix, a novel GnRH antagonist, has been shown to have lower histaminogenic potency and is the focus of this review.

Mechanisms of Action, Metabolism, and Pharmacokinetics Profile

In December of 2008, the FDA approved degarelix for the treatment of men with advanced PCa. Degarelix is administered as a monthly subcutaneous injection. It is a synthetic peptide that reversibly inhibits the hypothalamus-pituitary-gonadal axis by occupying the GnRH receptor without receptor activation. This results in decreased secretion of both LH and follicle-stimulating hormone (FSH) and subsequent testosterone decrease to castrate levels ($<$50 ng/dL). Broqua et al demonstrated the *in vitro* and *in vivo* pharmacological profile of degarelix in rats and monkeys.[15] This study found a dose dependent suppression of the pituitary gonadal axis as evidenced by the decrease in LH and testosterone. Unlike other GnRH antagonists, degarelix also demonstrated weak histamine releasing properties *in vitro* and had longer duration of action. In pre-clinical studies of PCa tumor growth, degarelix inhibited tumor growth in rat carcinoma models as effectively as surgical castration.[16] The pharmacokinetics of degarelix are described here as in the US prescribing information.[17] The metabolism of degarelix is primarily through peptide hydrolysis in the hepatobiliary system. Seventy to eighty percent of the metabolites are excreted in the feces as peptide fragments, while the remaining 20%–30% is renally excreted. The median plasma T ½ for depot formulation is 28–42 days dependent on the amount injected. Degarelix is distributed throughout total body water and *in vitro* plasma protein binding is estimated to be approximately 90%. When administered at a concentration of 40 mg/mL, degarelix demonstrates linear pharmacokinetics over the dose range of 120 mg–240 mg. Drug interactions with cytochrome P450 system are unlikely because degarelix is not a substrate and does not inhibit or induce the cytochrome P450 system.

Clinical Studies and Efficacy

Phase II dose finding studies were carried out in Europe and North America.[18,19] Van Poppel et al

reported their findings of the European open-label, randomized, parallel-group, dosage finding study with a primary endpoint of determining the proportion of patients with serum testosterone levels ≤0.5 ng/mL (defined as castrate level) at one month and monthly measurement up to one year.[18] This study randomized 180 patients to six treatment groups for one year. Patients were to receive one initial dose of 200 mg or 240 mg of degarelix and 12 monthly maintenance doses of 80 mg, 120 mg, or 160 mg of degarelix at a concentration of 40 mg/mL. Although both initial doses dropped testosterone levels to ≤0.5 ng/mL by day three, the 240 mg dose was shown to be the more suitable initial dose. By day three 92% of the 240 mg dose group had suppressed their testosterone level compared to 88% in the 200 mg dose group and at one month, a higher proportion of patients in the 240 mg dose maintain their suppressed levels (95% vs. 88%). Testosterone levels remained suppressed in 100% of patients in the 160 mg monthly maintenance dose group compared to the 80 mg and 120 mg doses (92% and 96%, respectively). Median testosterone level for the 147 patients who achieved testosterone levels ≤0.5 ng/mL at one year was 0.121 ng/ml (P25–P75 0.077–0.167). Prostate specific antigen (PSA) was reduced by 50% by day 14 and was maintained at low levels throughout the year for all study groups. At end of study, dihydrotestosterone (DHT) (83%–90%) and FSH (74%–88%) levels were also reduced. Gittelman et al reported their findings of the North American open-label, randomized, parallel-group study with the same primary end points as the European study.[19] One hundred twenty seven patients were randomized into two treatment arms for one year. Initial dose for all patients was 200 mg at a concentration of 40 mg/mL followed by 12 monthly maintenance doses of either 60 mg or 80 mg (concentration 20 mg/mL). After three days, testosterone was suppressed in 89% of patients and maintained at one month in 88% of patients. A higher proportion of patients (98%) maintained testosterone suppression for one year on the 80 mg dose vs. 93% for the 60 mg dose. It was noted in the study, that suppression levels of testosterone at one year were <0.1 ng/mL for both groups. A fifty percent reduction in PSA was also noted at 14 days and maintained at low levels in both treatment groups throughout the study. DHT and LH levels were also rapidly reduced and maintained.

The only phase III trial published to date randomized 620 patients to three treatment arms for one year; an initial degarelix dose of 240 mg followed by 80 mg maintenance dose (degarelix 240/80 mg), or an initial degarelix dose of 240 mg followed by160 mg maintenance dose (degarelix 240/120 mg), or leuprolide 7.5 mg dose monthly.[20] Primary endpoint of the study was testosterone suppression to castrate level as defined by ≤0.5 ng/ml from day 28 thru day 364. In an intention to treat analysis, the primary endpoint was achieved in 97.2%, 98.3%, and 96.4% of patients for the degarelix 240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively; therefore, proving the noninferiority and efficacy of degarelix when compared to leuprolide. Castrate levels of testosterone were achieved in >95% of patients in the degarelix groups at three days compared to a 65% increase in testosterone level from baseline in the leuprolide group. Microsurges in testosterone were noted in the leuprolide group at day 255 and 259 compared to no testosterone microsurges noted in the degarelix groups. FSH and LH decreased rapidly and remained suppressed until end of study in the degarelix group compared to an initial increase in LH and FSH in the leuprolide group with a subsequent decrease, however, the FSH level was noted to not decrease to the same extent when compared to the degarelix groups. The reduction from baseline in PSA at days 14 and 28 were statistically significant between the degarelix groups and leuprolide ($P = <0.001$). Based on these phase II and III studies the recommended doses and what has been approved by the FDA are an initial 240 mg dose followed by a monthly maintenance dose of 80 mg.[17]

Safety

The first approved GnRH antagonist, abarelix, was associated with a 1%–3% incidence of systemic allergic reactions,[14] in the phase III trial none of the patients receiving degarelix had systemic allergic reactions.[20] One year treatment of PCa with degarelix was generally well tolerated by patients.[18–20] Statistically significant side-effects between degarelix and leuprolide were found to be a higher rate of injection site reactions (40% vs. 1%, $P < 0.001$), lower rate of urinary tract infections (3% vs. 9%, $P < 0.01$), lower rate of arthralgias (4% vs. 9%, $P < 0.05$) and higher rate of chills (4% vs. 0%, $P < 0.01$). Reported injection

site reactions were noted predominantly after the initial injection and included pain, erythema, swelling, induration, and nodule.

Discussion and Conclusions

In certain clinical scenarios, such as in patients with localized PCa, the use of ADT is being brought into question due to the limited evidence on the impact in cancer-specific and overall survival. A population based cohort study of 19,271 men with clinical T1–T2 disease and >65 years old reported no improved survival with ADT when compared with conservative management.[6] Increasing awareness of the long term side effects from the use of ADT such as hot flashes, depression and cognitive impairment,[21] diabetes and coronary artery disease,[22] obesity,[23] osteoporosis and increased risk of fractures[24,25] has also brought into question the use of ADT in this patient population. In general, it is accepted that ADT is best suited for patients with clinically localized PCa undergoing radiation therapy where a survival advantage has been demonstrated[8,9] and in patients with advanced symptomatic metastatic disease. Although androgen deprivation can be achieved via surgical castration within 3 hours, pharmacological castration (range 8 hours to 60 days) is widely accepted by patients due to its psychological suitability and potential reversible nature. Manipulation of the hypothalamus-pituitary-gonadal axis mainly via the GnRH receptor is one area of research. GnRH analogues have been established as effective in reducing testosterone to castrate levels and in their use for ADT even with their initial testosterone surge, potential for testosterone microsurges, hormonal escapes, and inefficient suppression of FSH. The role in ADT with GnRH antagonists is an active discussion.[26–28] GnRH antagonists, such as degarelix, have been proven to be as effective and not inferior to GnRH analogues, such as leuprolide, in suppressing testosterone in a phase III trial.[20] Secondary endpoints demonstrated degarelix to have no initial testosterone surge, reach castrate levels of testosterone by day three, no testosterone microsurges, and to suppress FSH. Recently, a subset analysis on PSA progression of the phase III trial generated the hypothesis that patients receiving degarelix had a significantly lower risk of PSA progression or death compared to leuprolide ($P = 0.05$) although a limitation of the subset analysis was the small number of patients in each group.[29] Further studies are warranted to confirm these findings. To date there are no other randomized control trials and literature is sparse.

With these data, the question then becomes which patient population is best suited for GnRH antagonists. One could argue that the quick testosterone suppression achieved by day three without a testosterone surge makes degarelix the treatment of choice in a patient who requires rapid androgen suppression. An example would be a patient in whom a testosterone surge could result in detrimental outcomes such as those with impending spinal cord compression or long bone fracture or in patients with ureteral obstruction or retention and who would not be good surgical candidates. An alternative approach would be to use ketoconazole which causes castrate testosterone levels within 8 hours of administration[30] or leuprolide with antiandrogens blockade which has been proven to be effective in preventing the sequelae of the testosterone surge.[31,32] Another potential patient scenario for the use of degarelix is in patients on intermittent hormone therapy for their advanced PCa. Results from a European phase III study on intermittent hormone therapy with GnRH analogues in 766 patients with asymptomatic advanced PCa, demonstrated no reduction in survival and improved quality of life.[33] There are no published studies evaluating degarelix' use in intermittent therapy. A reasonable question to ask, given the lack of a testosterone surge, is whether degarelix would have a superior clinical impact on this patient population *vis a vis* cancer specific and overall survival. There are also several areas that have yet to be studied with degarelix such as the clinical significance of FSH suppression, progression free survival, cancer specific survival, and overall survival. Degarelix remains a reasonable choice for first-line therapy of patients in whom androgen deprivation therapy is indicated.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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