New Drug

Degarelix: A Gonadotropin-Releasing Hormone Antagonist for the Management of Prostate Cancer

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ABSTRACT

Background: Prostate cancer is the most commonly diagnosed cancer among men. Treatment can include surgery, radiation, chemotherapy, or hormonal manipulation. Gonadotropin-releasing hormone (GnRH) analogues are used to manage prostate cancer by desensitizing the stimulus to synthesize and release gonadotropins, such as luteinizing hormone (LH), which stimulate the synthesis and release of androgens, in turn stimulating the growth of prostate cancer cells. Although effective, these agents have limitations, such as a flare-up of cancer symptoms within the first 2 weeks of starting the drug.

Objective: This article reviews the pharmacology, pharmacokinetic and pharmacodynamic characteristics, and clinical data available on the newly approved drug degarelix for use in treating prostate cancer.

Methods: A search of the medical literature was performed in January 2009 with the databases MEDLINE and EMBASE (1950–present) and International Pharmaceutical Abstracts (1970–November 2008) using the terms *degarelix* and *FE200486*; follow-up searches using the same strategy were conducted in May 2009 and August 2009. Additional sources were identified by scanning available references and online journals and textbooks.

Results: GnRH antagonists, such as degarelix, offer clinicians another means to reduce the level of circulating androgens and limit this growth stimulus directed at malignant prostate tissue. Degarelix has been shown in animal studies to antagonize GnRH receptors in the pituitary gland, resulting in a significant reduction in circulating LH and a subsequent decrease in the synthesis of testosterone. Pharmacokinetic analysis suggests that upon subcutaneous administration, degarelix forms a gel depot, from which the drug then distributes to the rest of the body in a first-order manner. A Phase II study of the effect of degarelix in 187 men with prostate cancer found a loading dose of 240 mg to be not significantly better than 200 mg in reducing serum testosterone concentrations to ≤0.5 ng/mL within 3 days of dosing (200 mg, 88%; 240 mg, 92%). This difference in percentage of patients with testosterone suppression became statistically significant when measured again 1 month into the study (200 mg, 86%; 240 mg, 95%; $P = 0.048$). Evaluation of 80-, 120-, and 160-mg maintenance doses found all doses effective in maintaining suppression of testosterone, LH, and prostate-specific antigen (PSA); only minor differences were observed during the study period. In a Phase III study of 610 patients with prostate cancer, a loading dose of degarelix 240 mg SC followed by monthly maintenance doses of either 80 or 160 mg was compared with monthly doses of leuprolide 7.5 mg IM. Degarelix was found to be at least as effective as leuprolide in the ability to suppress serum testosterone to ≤0.5 ng/mL for up to 1 year (degarelix response rate, 80 mg, 97.2%; 95% CI, 93.5%–98.8%; degarelix 160 mg, 98.3%; 95% CI, 94.8%–99.4%; leuprolide response rate, 96.4%; 95% CI, 92.5%–98.2%). Other studies investigating various doses and schedules of degarelix have also been conducted. Adverse effects of degarelix in clinical trials were mild and relatively uncommon and included flushing reactions, injection-site pain, weight gain, and increases in serum transaminase levels.

Conclusions: Degarelix offers another option for chemical castration to reduce the androgenic growth stimulus on prostate cancer cells. The manufacturer of degarelix recommends a loading dose of 240 mg SC followed by the first monthly maintenance dose of 80

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mg 28 days later. Serum testosterone and PSA concentrations must be obtained to monitor the response during treatment with degarelix. (*Clin Ther.* 2009;31[Theme Issue]:2312–2331) © 2009 Excerpta Medica Inc.

Key words: degarelix, prostate cancer, GnRH, GnRH antagonist.

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer among men.[1] The American Cancer Society estimated in 2008 that >186,000 new prostate cancer cases were diagnosed and nearly 29,000 prostate cancer–related deaths occurred, representing 25% of all new cancer diagnoses and 10% of cancer-related deaths seen in men, respectively.[1] The overall incidence of prostate cancer in the United States between 2000 and 2004 was 160.8 cases per 100,000 men. Incidence patterns indicate that black men have a higher risk of developing prostate cancer than do their white counterparts.[1] Screening methods such as annual digital rectal exams (DREs) and measurement of serum prostate-specific antigen (PSA) concentrations have contributed to better rates of diagnosis.[2] These screening tools should be offered to all men by age 50 years, and by age 45 years for men at high risk, such as black men and those with a strong family history of the disease.[1–3]

If a patient is diagnosed with prostate cancer, treatment is not immediately initiated; instead, a plan of active surveillance is used. Treatment may be initially withheld until the cancer progresses or meets the criteria for intervention. Withholding initial treatment by using active surveillance avoids the occurrence of adverse effects from potentially unnecessary therapy, prolongs existing quality of life, and reduces the risks associated with treatment for otherwise indolent cancers. A downside to this strategy is the need for close and frequent monitoring, which may delay therapy that could otherwise stabilize the disease and allows time for the cancer to progress or metastasize, resulting in the need for more intensive treatment.[3]

If treatment for prostate cancer is initiated, generic options include surgery, radiation, chemotherapy, and androgen deprivation. Radiation may be delivered by external-beam radiotherapy targeted toward the prostate or pelvic lymph nodes or by the insertion of brachytherapy devices.[3] Surgical options include radical prostatectomy and/or pelvic lymph node dissection. Systemic chemotherapy regimens may include docetaxel with prednisone or estramustine, or mitoxantrone with prednisone.

Because of the hormone-dependent nature of the disease, prostate cancer can be treated with androgen deprivation therapy, achieved via surgical means (ie, bilateral orchiectomy) or medical means (ie, luteinizing hormone [LH]-releasing hormone agonists goserelin and leuprolide).[3] An additional pharmacologic mechanism for reducing androgen activity in prostate cancer is to use antiandrogens (ie, bicalutamide, nilutamide, dutasteride, finasteride).

Because of intolerable adverse effects and delayed onset of efficacy of existing therapies, clinicians are looking for additional means to treat patients with prostate cancer. One possible alternative treatment option is degarelix,* which reduces androgen concentrations through the antagonism of gonadotropin-releasing hormone (GnRH).[4] The objective of this review is to describe the unique pharmacology, pharmacokinetic and pharmacodynamic (PK/PD) characteristics, and clinical evidence that has been published on degarelix with regard to the management of prostate cancer.

METHODS

A search of the medical literature published between 1950 and the present was performed in January 2009 using MEDLINE and EMBASE. International Pharmaceutical Abstracts was searched for the period between 1970 and November 2008. The terms used in all searches included *degarelix* and *FE200486*. Results of the search were then limited to articles written in English. Online journals and reference lists from identified articles were searched individually for additional articles or abstracts. Follow-up searches using the same terms were performed in each database in May 2009 and again in August 2009 to identify additional studies that may have been published after the initial literature search. All clinical trials identified in the literature search were included in the following discussion. Background information on GnRH and its actions was gathered through searches of online textbooks to obtain the most recently published material. Ferring Pharmaceuticals, Inc. (Parsippany, New Jersey),

*Trademark: Firmagon® (Ferring Pharmaceuticals, Inc., Parsippany, New Jersey).

the manufacturer of degarelix, was contacted by telephone by the author twice in May 2009 to request additional drug information.

GONADOTROPIN-RELEASING HORMONE

The gonadotropic hormones include LH, follicle-stimulating hormone (FSH), and human chorionic gonadotropin and are classified as such because of their effects on the gonads.[5] Gonadotropin release from the anterior pituitary is mediated by intermittent pulses of GnRH, a neuroendocrine decapeptide from the hypothalamus that binds to GnRH receptors.[6,7] Upon binding GnRH, the G-protein–coupled GnRH receptor triggers the activation of phospholipase C and calcium ion mobilization, which subsequently activates protein kinase C isozymes, leading to stimulation of the synthesis of LH and FSH. In humans, GnRH is originally synthesized and released during the late fetal stages of development, but within 12 months after birth, the system undergoes a drastic reduction in activity, only to be reactivated shortly before puberty.[5] During puberty, pulses of GnRH release increase in amplitude and frequency until they reach the maintenance level seen in adulthood. Although GnRH is the major regulator of gonadotropin production, hormones that also have a small effect include gonadal steroids and inhibin-signaling proteins.

In males, LH stimulates the synthesis of androgens, such as testosterone, in the Leydig cells of the testes; FSH facilitates sperm maturation by stimulating the production of nutrients and proteins in the Sertoli cells. LH and FSH release can be suppressed with prolonged exposure to exogenously administered GnRH analogues (ie, LH-releasing hormone analogues), which drown out the typically intermittent GnRH stimulus, thus leading to desensitization and down-regulation of GnRH receptors within the pituitary. This process essentially creates a state of pharmacologic castration after a brief initial upsurge in gonadotropin release, termed a *flare-up*, from the high levels of exogenous administration of the agent. This flare-up increases the production of androgens, which then stimulate sensitive tissues including malignant prostate tissue, leading to an undesirable increase in symptoms felt by patients with prostate cancer.[5] Within 2 to 4 weeks after administration, the intended desensitization of the gonadotropic system occurs, leading to suppression of these compounds, a reduction in flare-up symptoms, and the potential for therapeutic benefit. Despite their measurable efficacy in prostate cancer, commercially available GnRH analogues have important disadvantages in the flare-up reaction and delay in hormonal suppression.[8]

In addition to GnRH analogues, modifications to the structure of GnRH have resulted in the development of GnRH receptor antagonist compounds with therapeutic utility. Antagonists such as ganirelix[6] and cetrorelix[9] are used to promote embryonic transfer and pregnancy after in vitro fertilization. Abarelix[10] was approved by the US Food and Drug Administration (FDA) in 2003 as the first depot injectable GnRH antagonist indicated for the palliative treatment of prostate cancer, but was voluntarily withdrawn from the US market in 2005 by the manufacturer for "economic reasons." Azaline B is another laboratory-modified molecule with GnRH antagonist activity that is often used for laboratory comparison with other GnRH antagonists, but has not been brought to market.[11] The difficulties with GnRH antagonists have been to find a formulation that provides slow release after injection, potent and long-lasting GnRH antagonism, and a mild adverse-effect profile.[8] In search of such an agent, Samant et al[12] synthesized additional peptide derivatives with various amino acid substitutions made on the GnRH molecule, one of which is now referred to as degarelix.

PROSTATE CANCER

The prostate is an organ located in the pelvic region between the bladder and external urinary sphincter of men.[13] Its location allows for palpation using digital insertion into the rectum. The prostate contains lobular glands that secrete components of the seminal fluid into the urethra. PSA is produced in secretory luminal epithelial cells, which also contain receptors for circulating androgens. Any portion of the prostate's 4 zones (central, peripheral, transition, and anterior fibromuscular stroma) can be affected by cancerous growth, but the most common site of malignant origin is the peripheral zone. The heterogeneous nature of tumors in the prostate complicates prognostic determination and treatment selection. Histologic examination simplifies these processes.[13]

The incidence of prostate cancer increases with each decade of life.[14] The median age at diagnosis is 68 years, and <10% of cases occur in patients aged <55 years.[15] When analyzed in age groups, 29.0%, 35.6%, 21.4%, and 4.7% of cases are seen in men

aged 55 to 64, 65 to 74, 75 to 84, and >84 years, respectively.[15] The dropoff in diagnoses in the oldest of men may be related to a reduction in the frequency of screening because of concomitant comorbid conditions that are considered more serious.[13] In addition to age, other factors that are believed to play a role in the development of prostate cancer include heredity, especially in men with 2 or more first-degree relatives with prostate cancer, and a diet high in saturated fats and red meat and low in fruits and vegetables. A link between higher androgen concentrations and the incidence of prostate cancer has also been postulated based on a correlation between higher testosterone levels and an increased frequency of prostate cancer in black men compared with both Japanese and white men.[16] Many men with prostate cancer are asymptomatic, and the disease is identified only after screening of PSA levels or upon autopsy.[13] Interestingly, although screening for prostate cancer has helped to identify individuals with the disease, a correlation between screening and survival benefit has never been established.[13,17] Nonetheless, the American Cancer Society currently recommends that men aged ≥50 years with a life expectancy of >10 additional years be offered PSA testing and DRE on an annual basis.[2] Those individuals at a higher risk of prostate cancer (ie, black men and men with at least 1 first-degree relative who developed prostate cancer before age 65 years) can begin screening by age 45, and men with multiple first-degree relatives who developed the disease at a younger age may begin screening as early as age 40.

Evaluation of PSA levels to screen for prostate cancer is a complex process that involves consideration of characteristics including the actual PSA serum concentration, the age of the patient, the PSA velocity, the PSA density, and the percentage of free PSA.[17] *PSA velocity* refers to the rate of rise in PSA over time, and this index therefore requires multiple tests over time for proper assessment. *PSA density* is the ratio of the PSA serum concentration to the volume of the prostate, as measured using transrectal ultrasound. PSA binds to a limited extent to serum proteins, but a portion remains as unbound free PSA in the serum. The percentage of free PSA is lower in men who have prostate cancer than in men who do not. If a PSA test is performed, a serum concentration of >4 ng/mL or an increase of >0.5 ng/mL per year warrants further diagnostic evaluation. Once a patient has been identified with prostate cancer, the prognosis is gauged from the Gleason score,[18] based on the histologic grade of differentiation as determined on pathologic examination of a prostate biopsy; the clinical stage (I–IV); and the patient's age at the time of diagnosis.[19,20] Patients deemed to have *localized disease* have prostate cancer confined to the prostate itself, whereas *advanced disease* describes patients in whom the cancer has spread to other tissue sites beyond the prostate.[13]

Management of prostate cancer is complex because only a portion of men diagnosed with the disease will actually die of it, and concerns about quality of life preclude some treatment alternatives in some patients. The decision to offer treatment is based on the risk posed by the cancer over time, weighed against the potential for benefit and harm from treatment.[20] Surgical intervention with radical prostatectomy to completely remove the cancer is used in men with a life expectancy of >10 years. Although techniques have improved, the risks of incontinence and erectile dysfunction warrant proper selection of patients. External-beam radiation is another option but carries the risk of bowel complications, such as diarrhea, as well as urinary and erectile problems.

Prostate cancers are different from most other cancers because of their susceptibility to hormones, namely androgens. The binding of androgens to androgen receptors is required for normal growth and differentiation of epithelial cells in the prostate.[21] Unfortunately, these same receptors are present on malignant prostate tissue and provide the same type of growth stimulus as in normal cells. Congenital mutations in the androgen receptor that inactivate it result in the lack of development of a prostate gland and the absence of prostate cancer.[22] This finding underscores the important role of androgens and their receptors in contributing to prostate cancer progression. This understanding has led to the development of agents that directly or indirectly interfere with the androgen receptor and induce a form of chemical castration; agents such as the antiandrogens, GnRH analogues, and now the GnRH antagonists offer new hope for controlling the disease.[23–26] When castration occurs via any means, normal prostate tissue atrophies and the products of prostate activity, such as PSA, are measurably reduced. Tumors in the prostate are likewise sensitive to the same methods of castration, and therefore PSA is monitored as an indicator of disease responsiveness. Unfortunately, treatment of prostate cancer is made more complex because changes can occur in the an-

drogen receptors on malignant cells that render androgen deprivation therapy ineffective. Castration-resistant prostate cancer can develop over time and indicates progression of the disease, as evidenced by rising PSA concentrations despite the continuation of previously effective treatment. Occasionally, the androgen receptors on malignant tissue undergo additional alterations such that the cells become able to use the exogenous molecules of treatment as agonists—ironically providing a growth stimulus—rather than as antagonists. When this occurs, withdrawal of the antiandrogenic agent can have a therapeutic benefit because of absence of the growth stimulus.[21]

The hormonal nature of prostate cancer and the therapeutic benefit of reducing androgen actions support the need to use agents that can affect this system. Use of an effective and well-tolerated GnRH antagonist that can ultimately reduce the stimulus for androgen synthesis offers another potential alternative in the management of prostate cancer.

DEGARELIX

Degarelix is a synthetically modified analogue of azaline B with GnRH antagonist activity. It was approved by the US FDA in December 2008 for the management of advanced prostate cancer.[12,27,28] Its effect against prostate cancer is based on the ability to block the GnRH receptor, thereby preventing the stimulus that would otherwise trigger the production and release of LH, which mediates the synthesis of androgens.[4] This action ultimately results in a reduction in circulating androgens, which provides a therapeutic benefit by reducing the growth stimulus used by hormone-sensitive malignant prostate tissue.[4]

Structure

Degarelix (FE200486, $C_{18}H_{107}ClN_{18}O_{18}$) is synthesized through a complex series of chemical reactions from *p*-methylbenzhydrylamine (MBHA) resin or a TentaGel S RAM resin (Rapp Polymere GmbH, Tübingen, Germany).[12,29,30] The end product of the reaction has a molecular weight of 1692.3116 Da.[29]

Previously synthesized GnRH antagonists are potent, but they lack other positive characteristics, such as ease of administration, to consider them clinically viable.[30] Advantages of degarelix compared with other molecules with GnRH antagonist activity include its high affinity and potency at the GnRH receptor, water solubility for an injectable formulation, and a longer $t_{1/2}$ after administration; all of these characteristics are believed to be related to the presence of additional hydrogen-bonding sites and the addition of urea and carbamoyl groups, which result in a slow diffusion from the site of administration.[29,30] The absence of in-vial gel formation upon reconstitution of powdered degarelix acetate is a formulation advantage compared with other GnRH antagonists; this issue has limited the application of other GnRH antagonists because of the need to inject these agents in a fluid form.[30]

While evaluating structural modifications to the basic MBHA resin, Jiang et al[30] found that several molecules synthesized in addition to degarelix also had the benefit of water solubility and lack of gel formation, but unfortunately had the disadvantage of causing histamine release and adverse effects upon administration. The ability to trigger histamine release is believed to be dependent on *N*-methylation at various positions along the molecules' chains; this is absent in degarelix. Other GnRH antagonist molecules, such as azaline B, cetrorelix, and ganirelix, have been observed to produce histamine release in rat mast cell models after administration at concentrations of <10 μg/mL. In contrast, degarelix requires administered concentrations of ≥100 μg/mL, a concentration similar to that seen with GnRH itself, to trigger histamine release. Therefore, better formulation and administration characteristics, the possibility of better tolerance, and positive in vivo study results suggest that degarelix has high potential for clinical trial evaluation.

Pharmacology

The pharmacologic characteristics of degarelix allow it to reduce the synthesis of downstream hormones (ie, androgens) and prevent their effects (ie, growth of malignant prostate tissue as evidenced by serum PSA concentrations). Broqua et al[8] used animal models to compare the in vitro and in vivo actions of degarelix with those of other GnRH antagonists, including abarelix, cetrorelix, ganirelix, and azaline B. In a set of mini-studies, degarelix was administered intravenously or subcutaneously to male rats and subcutaneously to ovariectomized female rhesus monkeys. Blood samples were obtained from all test animals to monitor serum LH, testosterone (rats only), and degarelix concentrations for PK evaluation. Harvested rat peritoneal mast cells incubated in vitro with degarelix for 2 minutes were used to evaluate histamine release.

After single-dose injections of degarelix 0.3 to 10 μg/kg SC in castrated male rats, reversible, dose-dependent reductions in plasma LH were observed (data not available).[8] When given to rats at higher doses of 12.5, 50, and 200 μg/kg SC, the onset of action and efficacy of degarelix in suppressing LH were similar to those of abarelix. The peak suppression of LH release (mean [SD]) occurred within 6 hours after administration of either drug, and no differences were observed among the 3 dosing levels of degarelix (12.5 μg/kg, 1.0 [0.04] ng/mL; 50 μg/kg, 1.0 [0.11] ng/mL; 200 μg/kg, 1.1 [0.11] ng/mL) or abarelix (12.5 μg/kg, 1.2 [0.18] ng/mL; 50 μg/kg, 0.9 [0.04] ng/mL; 200 μg/kg, 1.2 [0.15] ng/mL). Test animals given a vehicle control had LH concentrations of 12.0 (1.57) ng/mL at this same time point. Interestingly, although the duration of LH suppression increased with increasing doses of degarelix and was significantly longer for all doses of degarelix than for vehicle alone ($P < 0.05$, data not available) over the 7 days of monitoring, there was no dose-dependent increase in duration with abarelix. In fact, the plasma LH concentrations returned to control values within 24 hours after the abarelix injections. PK values for degarelix at doses of 50 and 200 μg/kg SC were as follows: absorption $t_{1/2}$, 4 and 30 minutes, respectively; T_{max}, 1 and 5 hours; and plasma disappearance $t_{1/2}$, 12 and 67 hours.

After administration of 200 μg/kg IV, the durations of LH suppression were determined for abarelix (12 hours), cetrorelix (12 hours), azaline B (24 hours), and degarelix (12 hours).[8] The duration of LH suppression for abarelix was the same as that observed after subcutaneous administration, whereas maximal LH suppression was maintained for 2, 3, and 6 days with cetrorelix, azaline B, and degarelix, respectively. When administered at a higher solution dose (2 mg/kg) prepared in 5% mannitol and injected at 20 μL SC per rat, degarelix was found to have a significantly longer duration of LH suppression than was azaline B (55 vs 14 days; $P < 0.05$). PK parameters for degarelix in this component of the study were absorption $t_{1/2}$, 2 minutes; T_{max}, 6 hours; and plasma disappearance $t_{1/2}$, 214 hours.

In ovariectomized rhesus monkeys given degarelix at doses of 0.045, 0.2, or 2 mg/kg SC, suppression of serum LH (concentration data not available) lasted for 2, 7, and 79 days, respectively.[8] PK parameters for the 0.045- and 0.2-mg/kg doses of degarelix in these animals included C_{max} of 39 ng/mL at 1 hour and 80 ng/mL at 3 hours, respectively, and serum disappearance $t_{1/2}$ of 80 hours (0.045 mg/kg) and 193 hours (0.2 mg/kg). The 2-mg/kg dose had a slower rate of absorption, requiring 24 hours to reach its C_{max} of 249 ng/mL. Although $t_{1/2}$ of degarelix for the 2-mg/kg dose was not reported, the drug was still measurable at day 41 (1.6 ng/mL), when maximum suppression of LH was still observed, and at day 101 (0.1 ng/mL), at which time LH concentrations returned to normal.

The amount of histamine released after administration of degarelix was quantified as a percentage of activity by the ratio of compound-induced histamine release (CIHR) to corrected total histamine.[8] CIHR was determined by subtracting the measured amount of spontaneous histamine release from the total amount of extracellular histamine release. Corrected total histamine was the amount of total histamine minus the level of spontaneous histamine release. In vitro evaluation of histamine release from rat peritoneal mast cells found that degarelix was associated with the lowest release of histamine (50% effective maximal concentration, 170 μg/mL) compared with cetrorelix (1.3 μg/mL), ganirelix (11 μg/mL), azaline B (19 μg/mL), and abarelix (100 μg/mL). This suggests that histamine release may be less of a concern with degarelix than with other GnRH antagonists.

To evaluate the testosterone-suppressing activity of degarelix as compared with abarelix, doses ranging from 0.3 to 10 μg/kg SC were given to male rats.[8] Although both agents were associated with a dose-dependent reduction in plasma testosterone concentrations, the minimum effective dose of degarelix to achieve this action was 1 μg/kg, whereas abarelix doses of ≥3 μg/kg were required for the same effect (data not available). To evaluate the duration of testosterone suppression, degarelix 2 mg/kg SC was compared with equal doses of azaline B, ganirelix, and abarelix. Compared with vehicle-treated rats, each agent was associated with statistically significant ($P < 0.05$) testosterone suppression (mean [SEM], vehicle only, 4431 [1546] pg/mL; degarelix, 61 [8] pg/mL; azaline B, 51 [9] pg/mL; ganirelix, 83 [10] pg/mL; abarelix, 51 [8] pg/mL) at day 1 after treatment. Surgically castrated rats receiving no additional intervention were also included in the evaluation for further comparison; these rats had testosterone concentrations of 3.6 (0.4) pg/mL at day 1. At day 7 after treatment, testosterone concentrations in the degarelix-treated group and the castrated rats remained low

(degarelix, 8 [2] pg/mL; castrated, 4 [1] pg/mL), whereas azaline B–treated rats (539 [254] pg/mL) showed some resolution, and both ganirelix-treated rats (2038 [475] pg/mL) and abarelix-treated rats (2310 [462] pg/mL) were returning to baseline. Azaline B was associated with below-baseline concentrations of testosterone up to day 14, whereas degarelix was associated with maintenance of the effect for up to 42 days, with values returning to normal at days 70 to 83.

To further assess the actions of degarelix, testosterone-sensitive organs of rats treated with 2 mg/kg SC were harvested at either 45 or 102 days after treatment.[8] In the group sacrificed at day 45, tissue weights of the prostate, seminal vesicles, and testes were reduced by 88%, 95%, and 86%, respectively (all, $P < 0.001$), compared with vehicle-treated rats. At day 102, the weights of prostate (35% reduction; $P < 0.001$) and seminal vesicles (29% reduction; $P < 0.001$) were still significantly lower than control values, whereas testicular weight was no different from that seen in the control rats.

To confirm the assumption that the mechanism of action of degarelix involves GnRH antagonism resulting in suppression of LH and testosterone release, 2 groups of male rats were given either a single injection of degarelix 2 mg/kg SC in 5% mannitol or control vehicle.[8] Doses of GnRH (0.01–100 μg/kg) were then given to all rats on days 7, 15, and 42. In response to the presence of GnRH, dose-dependent increases (data not available) in plasma LH were observed in both groups on days 7, 15, and 42, but testosterone release was measurable only on day 7. The inability of GnRH to stimulate testosterone release beyond day 7 may be associated with a functional impairment of Leydig cells due to prolonged LH suppression from degarelix exposure, causing atrophic changes in cellular morphology. The recovery of LH production in animals treated with degarelix indicates that the changes (ie, LH suppression due to blockade of GnRH receptors on the pituitary) are reversible.

The multiple studies performed by Broqua et al[8] suggest that degarelix offers the benefits sought in a GnRH antagonist, such as administration in a simple vehicle, favorable kinetics (eg, long tissue exposure), and beneficial PD effects (eg, rapid and prolonged suppression of LH and testosterone concentrations; physical decrease in the bulk of tissues sensitive to testosterone). The results also suggest that the subcutaneous route of administration is more promising than the intravenous route because of the longer duration of LH suppression, which the authors believe is due to the formation of a gel depot of drug that can then distribute throughout the body over a prolonged period. Finally, degarelix was associated with the least amount of histamine release among the GnRH antagonists tested; histamine release has been another limitation of previous commercially released products.

Pharmacokinetic and Pharmacodynamic Characteristics

Evaluation of the PK/PD characteristics of degarelix involves observation of the drug's measurable actions upon target pathways as well as the manner in which it is handled by physiologic processes. In specific terms, because gonadotropin and androgen production result from the binding of endogenous GnRH to the GnRH receptor, observing the ability of degarelix to antagonize GnRH at its receptor and suppress the release of these hormones would indicate the drug's ability to interfere with this system.

Jiang et al[30] evaluated the LH-suppressing ability and PK parameters of degarelix in rats. Plasma concentrations of degarelix were monitored for 90 days after a single bolus dose of 2 mg/kg SC. LH concentrations were concomitantly measured to assess the activity of degarelix and were found to be completely inhibited (data not available) shortly after degarelix administration up to day 41, with a gradual increase in LH over the remainder of the study period. Measurement of plasma concentrations of degarelix showed a C_{max} of 330 ng/mL by 6 hours after administration. The plasma concentration of degarelix at day 41 dropped to 6 ng/mL, and by day 48 to 3 ng/mL. This report suggests that suppression of LH release via antagonism of the GnRH receptor by degarelix is concentration dependent and is maintained as long as the serum concentration of the agent stays above ~5 ng/mL. Fortunately, subcutaneous administration of degarelix allows for a slow release from a postulated reservoir of gelled drug at the site of injection.[8,30,31] The formation of this drug depot has been confirmed by White et al[31] through imaging with contrast phase microscopy and infrared and nuclear magnetic resonance spectroscopy in rats given degarelix 2 mg/kg SC. The spontaneous creation of this degarelix gel depot upon subcutaneous injection results in distribu-

tive characteristics that mimic those of a drug with controlled-release properties and thus provides the sustained drug presence required to maintain concentration-dependent actions.[31]

The ability of degarelix to depress LH release in humans was confirmed by Tornøe et al,[32] who compared the LH release stimulated by triptorelin, a GnRH analogue, given at 3.75 mg SC or IV to 58 healthy men, with the suppression of LH release after administration of degarelix, given at doses ranging from 120 to 320 mg SC to 170 patients with prostate cancer. Triptorelin was associated with an increase in LH release to 1330 times the basal serum concentrations (data not available) and testosterone concentrations up to 77.5 times the basal amount. Degarelix was associated with a decrease in LH release of 94.2% (testosterone data not available).

Svensson et al[33] modeled the PK/PD properties of degarelix in an analysis of 60 healthy men. After the administration of a single subcutaneous dose of degarelix (dose amount not available), a terminal $t_{1/2}$ of 47 days was observed (**Table I**). The calculated value of competitive antagonism (K_i) of degarelix with endogenous GnRH at the GnRH receptor was 0.082 ng/mL. This prolonged antagonism reduced the number of receptors available for LH and testosterone synthesis; ~93% of receptors were fully suppressed. The mean residence time of receptor blockade was estimated at 4.5 days. These data support the claim that degarelix has GnRH receptor–blocking activity in humans.

Because of the complexities of dose-dependent antagonistic effects, proper dosing of degarelix requires an understanding of the PK properties of the drug after administration. The situation is complicated because of the formation of a subcutaneous depot of drug as a gel at the site of injection.[8] It is from this depot that degarelix then distributes throughout the body over a prolonged period. Several factors affect distribution from the depot, including volume and concentration of the injected solution and patient characteristics of subcutaneous composition. Tornøe et al[34] sought to clarify the PK properties of degarelix

Table I. Pharmacokinetic properties of degarelix after subcutaneous injection.

Parameter	Tornøe et al[34]	Svensson et al[33]	Jadhav et al[35]
Clearance, L/h	3.32	–	2.91
Volume of distribution of central compartment, L	8.88	–	11.4
Volume of distribution of peripheral compartment, L	40.9	–	–
Clearance between peripheral and central compartments, L/h	5.56	–	–
Absorption rate constant from drug depot to central compartment, L/h	0.211	–	–
Absorption $t_{1/2}$, h	32.9	–	–
Diffusion constant from inner to outer layer of depot, cm^2/h	6.03×10^{-6}	–	–
Fraction of subcutaneous dose in outer layer	0.147	–	–
Half-life from injection site ($t_{1/2,\ slow}$), d	–	–	1.17
Terminal half-life ($t_{1/2,\ fast}$), d	–	47	41.5–70.2
Competitive antagonism constant at GnRH receptor, ng/mL	–	0.082	–
Mean residence time of GnRH receptor blockade, d	–	4.5	–

GnRH = gonadotropin-releasing hormone.

and create a model to describe its physiologic pathway by conducting 2 Phase I studies. In the first study, degarelix was administered in 6 different doses to 48 healthy men who were randomly assigned equally to each treatment group; a seventh group of 8 men received only placebo. Dosing levels included 0.5, 2, 5, 10, 30, and 40 mg per participant, given in concentrations ranging from 5 to 30 mg/mL in volumes between 1 and 2 mL as single or twin injections. Blood samples were taken before each dose and then at 22 predetermined times for up to 59 days after administration. The second study involved intravenous administration of degarelix to provide a comparison for the subcutaneous evaluation. In this second phase, degarelix was administered in doses of 1.5, 6, 15, and 30 μg/kg IV to 24 men divided into 4 equal groups. The 2 lower doses were infused over 15 minutes, whereas the higher doses were given over 45 minutes. Blood samples were collected before each dose and at 13 predetermined times for up to 48 hours after completion of each infusion.

After intravenous administration, degarelix followed a first-order model of elimination from the central compartment.[34] After subcutaneous administration, however, the PK properties "flip-flopped" relative to the intravenous observations because of rate-limiting absorption that occurs from the injection site. This flip-flop effect occurs because of 2 rates of absorption, termed *fast* and *slow subcutaneous release*. According to the model, fast subcutaneous release provides rapid distribution of the drug to effector sites, whereas slow subcutaneous release allows for the prolonged effect due to absorption from the subcutaneous depot of gelled drug. The model assumes that after subcutaneous administration, drug accumulates in the tissue in concentric circles and moves at different rates from an inner layer to an outer layer. Drug is released from the outer layer to enter the systemic circulation, and this represents the fraction of fast subcutaneous release. The size and rate of movement of drug from the inner to the outer layer determine the slow subcutaneous release of the dose.

Using this model, the authors estimated the PK parameters of degarelix (**Table I**).[34] According to these results, the rate of drug diffusion from the subcutaneous depot appears to determine the rate-limiting step of drug disposition. Furthermore, the fraction of drug entering the outer layer of the depot provides the pulse for the initial fast release before gel formation is complete. Once the gel is formed, the slow-release phase begins. Favorable release of drug from this core is governed by the dose volume and dose concentration of drug injected at the site. For example, smaller injection volumes result in faster release because of the shorter distances required for drug to travel out of the depot area. In contrast, a maximum limit of injected volume can be reached, past which the gel depot takes too long to form, allowing too much drug to distribute before formation of the mature depot. Interestingly, bioavailability is inversely proportional to dose concentration, possibly because of the formation of a gel density that is not favorable for clinical disposition of the drug. The higher density of drug prevents release from the depot, leading to degradation of the agent before it reaches the systemic circulation. Factors that have yet to be assessed but may also be important in the PK properties of degarelix include the depth of injection, velocity of injection, temperature and pH of administered drug, and time elapsed from the reconstitution of degarelix to the injection. The authors identified a dose volume of at least 1 mL and a dose concentration of 30 mg/mL to optimize drug delivery. Tornøe et al are quick to point out that their model has mathematic limitations because of spatial factors proposed by the idea of only 2 layers of drug depot. They suggest that additional study of the drug disposition of labeled degarelix may provide further data to confirm their proposed model.

Additional evaluation of the PK/PD properties of degarelix was performed by Jadhav et al[35] to describe the drug's relationship to GnRH, LH, and testosterone after intravenous and subcutaneous administration and to predict the impact on testosterone concentrations after longer-term administration of degarelix. To evaluate the PD properties of degarelix and confirm the 2-compartment assumption, 3 small studies[35] were conducted. The first study involved 48 healthy men aged >65 years with normal serum concentrations of testosterone who were randomly assigned to 1 of 7 groups differing by dose (groups A to G, given 0, 0.864, 1.73, 3.7, 9.87, 24.7, and 49.4 μg/kg). Blood samples to measure degarelix, LH, and testosterone concentrations were obtained at baseline and at 15 additional times for up to 96 hours after the start of the intravenous infusion. In the second study, 24 healthy men with normal testosterone concentrations were randomly assigned to 4 treatment groups to receive

single degarelix doses of 1.5, 6, 15, and 30 µg/kg IV. Participants were monitored for 14 days, and blood samples were taken 17 times from baseline up to 10 days after the infusion.

As mentioned previously, the 2-compartment model assumes that after subcutaneous administration of degarelix, absorption occurs by both fast ($k_{a, fast}$) and slow ($k_{a, slow}$) first-order processes. To evaluate the kinetics in this system and confirm the hypothesized depot model, a third study[35] was designed involving the subcutaneous administration of degarelix to 80 healthy men with normal testosterone concentrations; participants were randomly assigned to 11 treatment groups with total doses escalating from 0.5 to 40 mg compared with placebo. Plasma concentrations of degarelix and serum concentrations of LH and testosterone were measured at baseline and at 22 additional times up to day 59 after the administration of study drug.

Results of the 3 studies by Jadhav et al[35] confirmed the findings previously published by Tornøe et al[34] in that degarelix displayed a biphasic pattern of disposition after either subcutaneous or intravenous administration. After subcutaneous administration, degarelix was released from the injection site, from the theorized in situ depot of drug accumulation, followed by a prolonged terminal phase. Because of the flip-flop kinetics after subcutaneous administration, drug was detectable up to 60 days after a single dose. After intravenous administration, however, absorption was slower relative to elimination, and drug was detectable for <4 days. PK parameters reported by Jadhav et al[35] are shown in **Table I**.

PD evaluation found that degarelix was associated with decreases in LH and testosterone in a concentration-dependent fashion.[35] LH concentrations achieved a nadir in ~0.5 day and then returned to baseline in a rebound effect by day 2. The duration of effect of degarelix was also found to be concentration dependent, with increasing doses associated with a slower recovery phase of LH. Mean PD parameters in the study population included the following: formation rate of LH ($k_{f, LH}$), 1.24 IU/L/h; pulsatile release of GnRH ($k_{rel, LH}$), 0.63 L/IU/h; LH degradation rate constants ($k_{deg, LH}$), 0.26, 0.24, and 0.22 per hour for groups A, D, and E of study 1, respectively; formation rate constant of testosterone ($k_{f, T}$), 0.68 L/h/IU; degradation rate constant for testosterone ($k_{deg, T}$), 0.26 per hour; and degarelix plasma concentration producing 50% of maximum inhibition of LH release, 0.45 µg/L. Baseline differences for LH concentration existed for groups A, D, and E, thus $k_{deg, LH}$ values are provided for each group.[35] These data quantify the effects of degarelix on the system in which it is introduced. Although these values are not typically considered in clinical practice, they show that degarelix has an important impact on the synthesis of LH and testosterone. This is the impact that may achieve a therapeutic benefit in patients with prostate cancer.

After distribution, degarelix undergoes peptide hydrolysis of ~70% to 80% of each dose in the hepatobiliary system, with eventual excretion in the feces; the remaining unchanged portion of drug is renally excreted.[4] The manufacturer states that the slow release of drug from the subcutaneous depot results in an overall elimination $t_{1/2}$ of 53 days. No active or inactive metabolites have been observed in samples of plasma obtained from patients given subcutaneous degarelix. The inclusion of men from several decades of life, including a large number of elderly men, has allowed study of the impact of age on the PK properties of degarelix, and no significant effects have been observed.

In Vivo Studies

Princivalle et al[36] evaluated the efficacy of degarelix in vivo compared with a standard of 2 GnRH analogues (leuprolide and triptorelin) in an experimental model of prostate cancer in rats transplanted with the Dunning R-3327H rat carcinoma. All treatments were initiated when tumor sizes reached ~300 mm^3 to ensure the absence of baseline differences. Triptorelin was administered at 0.5 mg/kg/d SC for up to 62 days. Degarelix was given at 1 mg/kg SC on a monthly schedule. Leuprolide was administered as depot injections of 1.5 mg/kg every 3 weeks until day 288. Two control groups of castrated and noncastrated rats given monthly subcutaneous injections of 5% mannitol were used for additional comparison. Blood samples to measure testosterone concentrations were taken on day 0 and on 15 additional predetermined days up to day 62. Antitumor activity was assessed by measuring tumor volume and weight as well as the weight of the testes, prostate, and seminal vesicles after the animals were sacrificed, which was at the end of the study period or earlier in the case of excessive tumor size. Evaluation was split into short-term effects, occurring with triptorelin and degarelix between days 0 and 62; and long-term effects, occurring with degarelix and leuprolide up to day 288.

Plasma testosterone concentrations in rats treated with triptorelin showed an initial flare-up to >20 ng/mL, then decreased slowly to castration levels (<25 pg/mL) at day 28 that were maintained to the end of this portion of the study at day 62.[36] A flare-up increase in testosterone was absent in rats given degarelix; castration levels were achieved at day 3 and maintained until study end. Measurement of the testes (mean [SD]) indicated significantly lower ($P < 0.01$) mean weights in rats treated with degarelix (410 [40] mg) than in those treated with triptorelin (900 [120] mg). Noncastrated control rats had a mean testes weight of 2650 (250) mg. No significant differences were found in the weights of seminal vesicles (triptorelin, 100 [20] mg; degarelix, 100 [30] mg) or prostates (triptorelin, 40 [10] mg; degarelix, 30 [20] mg). Tumor volume was significantly lower ($P < 0.01$) in the degarelix group (326 [87] mm^3) than in triptorelin-treated animals (818 [413] mm^3) and was similar to that seen in castrated rats (351 [174] mm^3). Compared with control rats, degarelix was associated with significantly smaller tumor volumes beginning on day 21 and continuing until day 62 (degarelix, 326 [87] mm^3; control, 2295 [1035] mm^3; $P < 0.01$). Triptorelin was not associated with a measurable reduction in tumor volume compared with control rats up to day 38, but a difference was achieved by day 49 and was maintained until study end. By the completion of the study, tumor weights in degarelix-treated rats (370 [120] mg) were similar to those in castrated controls (310 [150] mg) but were significantly smaller ($P < 0.01$) than tumors extracted from triptorelin-treated rats (1340 [750] mg).

In the longer-term portion of the trial, degarelix-treated rats reached castration levels of testosterone within 2 days after administration and maintained this concentration until day 343, well beyond the initially planned termination of the study.[36] On the other hand, in rats treated with leuprolide, testosterone concentrations showed a predictable flare-up, followed by suppression to castration levels within 1 month (data not available). This effect of leuprolide was finite, and all rats in both the control and leuprolide groups had to be euthanized by day 223 because tumor growths reached a maximum size felt ethically intolerable for the test animals. In animals treated with degarelix, tumor suppression occurred almost immediately after drug administration, evidenced by tumor shrinkage similar to that seen in castrated rats (data not available). In rats treated with leuprolide, however, a delay of ~1 month was observed before tumor suppression was identifiable. The mean (SD) tumor volume of leuprolide-treated animals at the time of sacrifice was 2489 (1063) mm^3, whereas the degarelix and castration groups had volumes of 666 (291) mm^3 and 820 (552) mm^3, respectively, at day 223 (statistics not available). At the end of the observation period on day 343, tumor volumes were similar in animals treated with either agent (degarelix, 2140 [1165] mm^3; leuprolide, 1897 [1391] mm^3; statistics not available).

The actions reported by Princivalle et al[36] mirror the results reported by Broqua et al[8]; both provide evidence of highly effective tumor-suppressing activity in rats related to antagonism of GnRH, resulting in rapid reductions in circulating concentrations of LH and testosterone. Comparison with leuprolide shows that degarelix is associated with a similar ability to manage tumor size and similar values of drug activity. One of the benefits of degarelix appears to be the rapid onset of action compared with leuprolide, which can take weeks to mount a measurable response. The multiple mini-trials completed by the respective authors provide a solid picture of the PD properties of degarelix. Clearly, one hopes that the success of degarelix observed in the laboratory can be extrapolated to the human population affected by prostate cancer.

Clinical Efficacy

The outcome metrics used to determine the activity of agents against prostate cancer are somewhat different from those used to assess the activity of traditional chemotherapy used in many other cancers. Rather than the common measures of objective response (eg, complete or partial response as evidenced by radiographic images) or overall survival or progression-free survival, more desirable outcomes in prostate cancer management include results such as the degree of testosterone suppression and the degree of PSA reduction. As mentioned previously, the low likelihood that patients with prostate cancer will actually die of the disease makes these outcomes more reasonable, and the clinical trials designed to evaluate the activity of degarelix in patients with prostate cancer have used these outcomes. It should be noted that although these measures help identify whether the agent is physiologically affecting a prostate tumor, they offer only an indirect representation of treatment success. None-

theless, these outcomes are the current indicators of choice.

Tammela et al[37] evaluated the efficacy of a single dose of varying strengths and concentrations of degarelix in treating men with prostate cancer. This Phase II multicenter, randomized, dose-escalating study involved single subcutaneous injections of degarelix 120 mg (20- and 40-mg/mL solutions), 240 mg (40- and 60-mg/mL solutions), and 320 mg (60-mg/mL solution) given to 172 men aged 48 to 89 years with a median PSA concentration of 38 ng/mL and a median testosterone concentration of 4.16 ng/mL. Thirty-one percent (53/172) of the men had metastatic disease, 36% (62/172) had advanced localized disease, 26% (45/172) had local disease, and 7% (12/172) were not staged. Gleason scores[18] of the participants were 2 to 4 in 18% (31/172), 5 to 6 in 57% (98/172), and 7 to 10 in 25% (43/172). Among the 169 patients evaluable for response, the 240-mg (40-mg/mL) dose was associated with the highest percentage of patients (96%) meeting the target outcome of testosterone suppression to ≤0.5 ng/mL, observed at days 3 and 28. The percentages of patients meeting this outcome at days 3 and 28 for the remaining doses were 96% and 88% (20 mg/mL) and 75% and 65% (40 mg/mL) for 120-mg doses, respectively; 88% and 63% for 240 mg in the 60-mg/mL solution; and 96% and 89% for the 320-mg dose given as a 60-mg/mL solution. No patients required discontinuation from the study because of adverse effects, although 5% reported pain at the injection site and 3% reported erythema. The most common adverse effects (data not available) were related to androgen deprivation (not otherwise specified).[37] Although this was a short-term study, it provides an opportunity to observe the rapid hormonal effects induced by degarelix at multiple doses and solution concentrations. Furthermore, the results support the idea that proper formation of the gel depot, resulting in optimal PK properties and efficacy, is dependent on both the concentration and dose of subcutaneously administered degarelix.

Gittelman et al[23] conducted a Phase II open-label, randomized, dose-finding trial to evaluate the efficacy of several doses of degarelix in the treatment of prostate cancer. In this study, men aged ≥18 years with adenocarcinoma of the prostate in any stage were given a starting dose of degarelix 200 mg followed by 12 monthly maintenance doses of either 60 or 80 mg. All patients had baseline testosterone concentrations of >2.2 ng/mL (ie, the lower limit of normal) measured within 3 months of study initiation. Previous use of hormonal therapy disqualified potential participants, except for patients who had received these agents as adjunctive therapy in combination with prostatectomy or radiotherapy for a maximum of 6 months, with curative intent. The primary end point of the trial was the number of patients who were able to achieve and maintain a serum testosterone concentration of ≤0.5 ng/mL at all monthly measurements during the year-long study in response to treatment with degarelix. Additional end points included the percentage of patients with testosterone concentrations ≤0.5 ng/mL by study day 3; the time to 50% and 90% reductions in PSA; the time to progression (ie, rise in PSA levels after initial suppression); and changes in PD parameters of serum testosterone, PSA, dihydrotestosterone (DHT), LH, and FSH during the study period.

Although 127 men were randomly assigned to receive study treatment, 23 were excluded from efficacy analysis because of protocol violations; they were retained in the intent-to-treat and tolerability analyses.[23] Of the original cohort of 127 patients, 63 patients (median age, 76 years; range, 48–87 years) received the 60-mg maintenance dose and 64 patients (median age, 76 years; range, 47–93 years) received the 80-mg dose. Only 57 and 47 patients were included in the efficacy analysis in the 60- and 80-mg maintenance dosing groups, respectively. In total, 87 of 127 patients (69%) received all study doses (60 mg, 42/63 [67%]; 80 mg, 45/64 [70%]). Reasons for early termination from both treatment groups included inadequate testosterone suppression (16/127 [13%]), adverse effects (6/127 [5%]), withdrawal of consent (5/127 [4%]), noncompliance (5/127 [4%]), investigator decision for withdrawal (4/127 [3%]), and unspecified (4/127 [3%]). By day 3 after the starting dose of degarelix, 90% of patients (57/63; 95% CI, 79% to 96%) in the 200/60-mg group and 89% (57/64; 95% CI, 78% to 95%) in the 200/80-mg group had suppression of testosterone to ≤0.5 ng/mL. This small difference between treatment arms was not statistically significant. Among those patients who achieved a testosterone concentration of ≤0.5 ng/mL by the first month and were monitored for the full year, 93% (42/45; 95% CI, 82% to 99%) of patients in the 200/60-mg group and 98% (41/42; 95% CI, 87% to 100%) in the 200/80-mg group (absolute dif-

ference, 4.29%; 95% CI, –7% to 17%; *P* = NS) maintained testosterone below the target for the full study period. Median times to 50% and 90% reductions in serum concentrations of PSA were 14 days (200/60 mg, range, 3–84 days; 200/80 mg, range, 1–56 days) and 56 days (200/60 mg, range, 28–168 days; 200/80 mg, range, 14–252 days), respectively, in both groups. Progression of PSA concentrations was observed in 5 of 63 patients (8%) in the 200/60-mg group by a median of 196 days (range, 107–280 days) and in 4 of 64 patients (6%) in the 200/80-mg group by a median of 154 days (range, 28–308 days). The most common adverse effects in the 200/60-mg and 200/80-mg groups were attributed to androgen deprivation and included hot flushes (24/63 [38%] vs 31/64 [48%]) and fatigue (10/63 [16%] vs 15/64 [23%]). The overall incidence rates of reported adverse effects were 87% (55/63) and 81% (52/64) in the 200/60-mg and 200/80-mg groups, respectively. The adverse effects were rated as mild to moderate in the majority (87%) of cases. Severe adverse effects included 3 patients with myocardial infarction, 1 patient with injection-site urticaria, 1 patient with deep vein thrombosis, and 1 patient with asthenia; each of these patients was withdrawn from the study. Serum concentrations of alanine aminotransferase increased in 16% (10/63) of the 200/60-mg group and 33% (21/64) of the 200/80-mg group, but concentrations did not exceed 3 times the upper limit of normal in any patient. Although a small number of patients were observed to have PSA progression after an initial response to degarelix, this study found that most patients treated with a starting dose of 200 mg followed by either 60- or 80-mg monthly doses for up to 1 year achieved rapid testosterone suppression that was maintained over the treatment period.

Gittelman et al[24] presented findings in abstract form from a multicenter, randomized, dose-ranging study of degarelix in 310 evaluable patients with histologically confirmed prostate cancer and serum PSA ≥2 ng/mL. Demographic characteristics included a median age of 73 years (range, 47–93 years); the median baseline serum testosterone concentration was 4.1 ng/mL, and median PSA was 20 ng/mL. With regard to cancer staging, 19% (59/310) of patients were considered to have metastatic disease, 24% (74/310) had locally advanced disease, 30% (93/310) had localized disease, and 27% (84/310) were not staged. Two degarelix loading doses of either 200 mg (n = 218) or 240 mg (n = 92) SC were administered. Among patients treated with the higher loading dose, 92% (85/92) achieved a serum testosterone concentration of ≤0.5 ng/mL on day 3, and 95% (87/92) met this outcome on day 28. Only 87% (190/218) given the lower loading dose achieved a serum testosterone concentration ≤0.5 ng/mL by day 28 (day-3 data not available for 200-mg dose). Of the 4 different maintenance dosing levels (ie, 60, 80, 120, and 160 mg) beginning 28 days after the loading dose, all patients (49/49) given the 160-mg monthly dose maintained serum testosterone concentrations ≤0.5 ng/mL, with no evidence of hormonal surge, during the 364-day study period. Only 89% of patients (40/45) given 60-mg monthly maintenance doses achieved this outcome, as did 98% (42/43) of those given 80 mg per month as a 20-mg/mL injection, 92% (44/48) given 80 mg as a 40-mg/mL injection, and 96% (48/50) given the 120-mg injection. PSA decreased by 90% at week 8, 94% at week 12, and 96% at week 24 in patients given the 160-mg maintenance dose. (Values for other dosing regimens are unavailable.) Twelve patients (6%) from all dosing schema withdrew from the study because of adverse effects, most of which were attributed to androgen deprivation. Although the data from this abstract are not complete, they show that degarelix has a profound and rapid effect in reducing testosterone synthesis and PSA concentrations. The higher loading dose of 240 mg induced a clinically measurable difference in testosterone suppression, and the higher maintenance dose preserved this response over the year-long evaluation period. The remaining doses provided a potent effect as well. Despite these measurable differences, additional evaluation of the combination of doses is needed, and the impact on patient care remains unclear.

Another multicenter, randomized, dose-finding Phase II study was performed by Van Poppel et al[25] to evaluate the tolerability and efficacy of 2 different loading doses of degarelix (200 mg vs 240 mg), each combined with 3 different maintenance doses (80, 120, and 160 mg). The investigation was performed with an open-label, parallel-group design. Men aged ≥18 years with any stage of prostate cancer, a baseline serum testosterone concentration of ≥2.2 ng/mL, an Eastern Cooperative Oncology Group score of ≤2,[38] and a PSA concentration of ≥2 ng/mL were randomly assigned to 1 of 6 subcutaneous dosage regimens (loading dose/maintenance dose: 200 mg/80 mg, 200 mg/120 mg, 200 mg/160 mg, 240 mg/80 mg, 240 mg/120 mg, or 240 mg/160 mg). Patients were excluded

if they had received hormonal therapy, except for patients who were given curative-intent prostatectomy or radiotherapy with hormonal therapy for a maximum of 6 months, at least 12 months before randomization. The primary objective of efficacy was determined with serum testosterone measurements at monthly visits for up to 1 year.

Although 189 men were originally randomized, 6 were removed from further evaluation because of protocol violations and lack of treatment administration.[25] Additional withdrawals due to insufficient testosterone response (16/189 [8%]), adverse effects (13/189 [7%]), and other reasons (13/189 [7%]) resulted in a population of 141 men who completed the study (200/80 mg, n = 20; 200/120 mg, n = 21; 200/160 mg, n = 25; 240/80 mg, n = 27; 240/120 mg, n = 27; 240/160 mg, n = 21). In the intent-to-treat population of 187 men, demographic characteristics were comparable among the 6 treatment groups and included the following: age (median, 72 years; range, 52–93 years), race (180 white [96%], 6 black [3%], and 1 Asian [<1%]), body mass index (median, 26 kg/m^2; range, 18–41 kg/m^2), weight (median, 77 kg; range, 50–150 kg), baseline testosterone concentration (median, 4.13 ng/mL; range, 3.37–5.19 ng/mL), baseline PSA concentration (median, 27.6 ng/mL; range, 12–55 ng/mL), stage of disease (41 localized [22%], 60 locally advanced [32%], 36 metastatic [19%], 50 not classifiable [27%]), and Gleason scores[18] (available in 185 patients; 2–4, n = 36 [19.5%]; 5–6, n = 76 [41%]; 7–10, n = 73 [39.5%]). By day 3, a total of 88% and 92% of patients receiving the 200- and 240-mg loading doses of degarelix, respectively, had achieved testosterone concentrations ≤0.5 ng/mL. The difference between the groups became statistically significant by 1 month into the study, at which time 86% (81/94) of patients who had received the 200-mg dose maintained testosterone at ≤0.5 ng/mL, versus 94% (87/93) in the 240-mg dose group (95% CI, 1.010–6.651; P = 0.048). Pooling the results in groups based on maintenance dose regardless of loading dose found sustained testosterone concentrations ≤0.5 ng/mL in 92% (80 mg, 44/48), 96% (120 mg, 48/50), and 100% (160 mg, 49/49) of patients from month 1 until the end of the study. Decreases in DHT (reduction range, 83%–90%; data not available) and FSH (reduction range, 74%–88%; data not available) were also observed during treatment. LH concentrations also decreased, with a reduction of >80% observed (data not available) across all treatment groups just 1 day after administration of the first dose of degarelix. Upon completion of the study, the median decrease in LH from baseline was 92% to 95% for all men (data not available). The median time for PSA concentrations to decline by 50% was 14 days (overall range, 7–28 days) in all 6 dosing groups. The median time to reach a 90% reduction in PSA concentrations was 56 days in all groups (overall range, 56–224 days), except among patients who received the 80-mg maintenance dose, in whom it took a median of 84 days (group range, 56–168 days) to reach this threshold. In considering specific PSA goals after 6 months of treatment, between 69% and 95% of patients reached concentrations of <4 ng/mL, and 31% to 48% reached concentrations of ≤0.4 ng/mL. Percentages of patients who reached these concentrations at 12 months were not available. In the intent-to-treat population, 14 patients (7%) distributed among 5 of the dosing groups (none in the 200/80-mg group) experienced progression of their PSA concentrations during the investigation. The number of patients and median number of days to PSA progression in these 5 groups were as follows: 200/120 mg, 3/32 (9%) and 224 days (range, 140–308 days); 200/160 mg, 1/32 (3%) and 308 days; 240/80 mg, 4/30 (13%) and 280 days (range, 252–336 days); 240/120 mg, 4/33 (12%) and 224 days (range, 126–364 days); 240/160 mg, 2/30 (7%) and 140 days (range, 140–140 days).

This study shows that degarelix was associated with a rapid and sustained reduction in serum testosterone and PSA, as well as FSH and LH.[25] Evaluation of the 200- and 240-mg loading doses in this study, along with the results of Gittelman et al,[23] suggests that the 200-mg starting dose may be less effective than the higher dose in achieving castration levels of testosterone. This is consistent with the dose-dependent effect observed in animal studies. With regard to the different maintenance doses, there was little variation in measurable response between 80, 120, and 160 mg. This may suggest that once the gel depot is formed from the loading dose, the 80-mg dose is adequate to maintain the concentration of hormonal manipulation considered clinically relevant to controlling the disease. Finally, as noted in previous studies, the finding of a minority of patients who either did not respond or could not maintain a response over the duration of the trial may suggest that other factors, as yet unidentified, may affect the response to treatment.

Degarelix has also been compared with currently available hormone-manipulating modalities. Klotz et al[26] performed a Phase III comparative, randomized, open-label, parallel-group evaluation of the tolerability and efficacy of degarelix compared with leuprolide in men with any stage of prostate cancer. Of the 610 patients randomly assigned to treatments, all patients receiving degarelix were given a starting dose of 240 mg SC. Maintenance doses of degarelix were either 80 mg SC (arm A; 207 patients) or 160 mg SC (arm B; 202 patients) given as 12 monthly doses. Leuprolide was given as 12 monthly injections of 7.5 mg IM to 201 patients. Patients receiving leuprolide could receive bicalutamide (23/201 [11%]) at the clinicians' discretion to moderate flare reactions occurring at the start of treatment. Median ages were 72 years in the degarelix arms (arm A, range, 51–89 years; arm B, range, 50–88 years) and 74 years in the leuprolide arm (range, 52–98 years). Patients with localized disease at baseline numbered 69 of 207 (33%) in the degarelix low-dose arm, 59 of 202 (29%) in the degarelix high-dose arm, and 63 of 201 (31%) in the leuprolide arm. Localized advanced disease without metastasis was observed in 64 of 207 patients (31%) in arm A, 62 of 202 patients (31%) in arm B, and 52 of 201 patients (26%) taking leuprolide; respective rates of metastatic disease were 37 of 207 (18%), 41 of 202 (20%), and 47 of 201 (23%). The remaining patients in each arm had disease that was not classifiable.

The primary efficacy end point was the ability of either drug to provide a cumulative probability of suppressing serum testosterone concentrations to ≤0.5 ng/mL as measured at monthly intervals up to day 364.[26] Both doses of degarelix were associated with this level of suppression (arm A, 97.2%; 95% CI, 93.5%–98.8%; arm B, 98.3%; 95% CI, 94.8%–99.4%), as was leuprolide (96.4%; 95% CI, 92.5%–98.2%). Among the patients, 5 of 207 (2%), 3 of 202 (2%), and 7 of 201 (4%) termed *escapers* had at least 1 monthly testosterone concentration >0.5 ng/mL in degarelix arms A and B and the leuprolide group, respectively. Insufficient testosterone suppression was seen in a total of 12 men: 4 of 207 (2%) and 2 of 202 (1%) in degarelix arms A and B, respectively, and 6 of 201 (3%) receiving leuprolide. With regard to median testosterone concentrations at day 3, patients in both degarelix groups (240/80 mg, 0.24 ng/mL; 240/160 mg, 0.26 ng/mL) achieved significantly lower values than did patients receiving leuprolide (6.3 ng/mL; $P < 0.001$). Furthermore, 96.1% of patients in arm A and 95.5% in arm B (data not available) reached serum testosterone concentrations ≤0.5 ng/mL by day 3, whereas none of the patients receiving leuprolide reached this value. Among patients who received leuprolide and were not given bicalutamide, 144 of 178 (81%) had a surge in testosterone of ≥15% from baseline within the first 2 weeks of treatment. Degarelix and leuprolide provided similar tolerability; serious adverse effects were observed in 21 of 207 patients (10%) and 24 of 202 patients (12%) in degarelix arms A and B, respectively, and in 28 of 201 patients (14%) in the leuprolide group. These adverse effects (not specified) prompted discontinuation of study medication in 15 of 207 patients (7%) in degarelix arm A and 19 of 202 patients (9%) in arm B, and in 12 of 201 patients (6%) receiving leuprolide. These data suggest that degarelix was at least as effective as leuprolide in reaching and maintaining the therapeutic indicator. The rapid suppression and absence of testosterone surge may indicate additional advantages of degarelix. Although these data are promising, this study is limited by the relatively short observation period and the lack of any survival data or validated quality-of-life measures.

Tolerability

Van Poppel et al[25] reported adverse effects during degarelix use that were consistent with androgen deprivation. Among the 187 patients given study medication and included in the tolerability analysis, the most common (≥10%) adverse effects included hot flushes in 62 patients (33%) and injection-site pain in 18 patients (10%). **Table II** presents a complete list of adverse effects. Adverse effects that were graded as severe occurred in 21 of 187 patients (11%). Thirteen patients (7%) required discontinuation of study drug because of disease progression, cardiovascular events, cerebrovascular accident, cachexia, elevated liver enzymes, bronchopneumonia, and laryngeal cancer, but none of these events were believed to be related to degarelix use. Furthermore, despite the deaths of 11 patients (6%) during enrollment in the study, none of the deaths were considered to be associated with degarelix. Although the overall incidence of adverse effects was relatively low, it should be noted that study medication was provided for only 1 year, and the patterns of adverse effects that would occur after a longer period of dosing remain undetermined.

According to the manufacturer, the most common adverse effects observed in 409 patients treated with

Table II. Frequency of adverse effects of degarelix at various doses in 187 men with prostate cancer monitored for 1 year. Data are presented as number (%).

	Dose*						
Adverse Effect	200/80 mg (n = 30)	200/120 mg (n = 32)	200/160 mg (n = 32)	240/80 mg (n = 30)	240/120 mg (n = 33)	240/160 mg (n = 30)	Total (N = 187)
Hot flushes	14 (47)	8 (25)	10 (31)	11 (37)	9 (27)	10 (33)	62 (33)
ALT increase	3 (10)	1 (3)	3 (9)	0	1 (3)	1 (3)	9 (5)
Back pain	2 (7)	3 (9)	2 (6)	1 (3)	2 (6)	1 (3)	11 (6)
Cough	2 (7)	1 (3)	2 (6)	1 (3)	0	3 (10)	9 (5)
Fatigue	2 (7)	1 (3)	2 (6)	3 (10)	1 (3)	2 (7)	11 (6)
Urinary tract infection	2 (7)	2 (6)	2 (6)	2 (7)	2 (6)	1 (3)	11 (6)
Diarrhea	1 (3)	3 (9)	2 (6)	0	1 (3)	2 (7)	9 (5)
Injection-site pain	1 (3)	3 (9)	0	6 (20)	6 (18)	2 (7)	18 (10)
Weight increase	0	3 (9)	4 (13)	4 (13)	3 (9)	2 (7)	16 (9)

ALT = alanine aminotransferase.
*Loading doses of 200 or 240 mg and maintenance doses of 80, 120, or 160 mg.
Reprinted with permission.[25]

degarelix were injection-site reactions (eg, pain [28%], erythema [17%], swelling [6%], induration [4%]), hot flashes (26%), increased weight (10%), fatigue (4%), and alterations in serum transaminases (10%).[4] The manufacturer also suggests that a decrease in bone density may be possible with long-term use of degarelix, as has been observed with other GnRH adulterating means (eg, orchiectomy, GnRH agonists), but this has not yet been documented in clinical use of degarelix. The manufacturer also warns about QT prolongation observed in patients undergoing androgen deprivation. This warning is based on the report by Klotz et al[26] that 3 of 409 patients (<1%) receiving degarelix and 4 of 201 patients (2%) receiving leuprolide had a Fridericia-corrected QT interval of ≥500 milliseconds. Therefore, patients with existing cardiac concerns, such as congenital long-QT syndrome, electrolyte abnormalities, congestive heart failure, or pharmacologic management of cardiac rhythm, should undergo proper evaluation and consideration before starting treatment with degarelix.[4] Antibody formation has also been observed with degarelix use, but the clinical impact has yet to be determined.

Because of the effects of degarelix on GnRH-dependent systems in men as well as women, it is considered a category X agent, meaning that women who are or may become pregnant should not be exposed to this agent.[4]

Drug Interactions

No reports of drug interactions with degarelix were identified in a search of the literature. Furthermore, degarelix has not been shown to be a substrate for any cytochrome P450 enzymes; nor does it inhibit or induce the activity or amount of any of these enzymes.[4] Whether degarelix is affected by or contributes to any PK alterations of any other drugs remains to be determined. Additional studies would be valuable to assess whether any specific drugs or conditions alter the PK properties of degarelix.

Dosage and Administration

The FDA approved degarelix for the treatment of patients with advanced prostate cancer in December 2008. Degarelix has also been commercially available

in Europe since March 2009.[39] Degarelix is available as a powder of the acetate salt and mannitol and requires reconstitution with sterile water for injection to a concentration of 40 mg/mL before administration.[4] The recommended loading dose of degarelix is 240 mg, administered as 2 injections of 120 mg SC. Monthly maintenance doses of 80 mg as a 20-mg/mL solution should be started 28 days after the loading dose. The manufacturer recommends administering degarelix subcutaneously into the abdominal region, away from the ribs and any areas subjected to pressure (eg, under a waistband or belt), and varying the site periodically.

Although ~20% to 30% of degarelix is excreted as unchanged drug in the urine, there are no studies on renal impairment and therefore no data to indicate that a dose reduction of the agent is required in patients with renal dysfunction.[4] Likewise, limited study of degarelix is available in patients with hepatic impairment. The manufacturer states that exposure to degarelix has been observed to decrease by 10% and 18% after a 1-mg intravenous dose given to non–prostate cancer patients with Child-Pugh scores of A and B, respectively. Patients with severe hepatic impairment (ie, Child-Pugh score of C) may therefore require additional monitoring to determine the degree of medical castration, as a further reduction in drug exposure may limit the clinical activity of degarelix. Practitioners should use caution when administering degarelix to patients with a creatinine clearance <50 mL/min or with severe hepatic impairment.

Pharmacoeconomics

No studies were found in the literature search on the impact of degarelix on the economics of caring for patients with prostate cancer. A cursory analysis can be made to compare the costs of treating a patient with prostate cancer with degarelix or GnRH analogues. The average wholesale cost of degarelix in May 2009 was ~$1120 for the 240-mg loading dose and $373 per month of maintenance dosing thereafter.[40] This would give a 12-month cost of >$5200. A 12-month course of leuprolide acetate 7.5 mg would cost nearly $10,000, while the same course of goserelin acetate 3.6 mg would cost ~$5400. Degarelix might allow additional minor cost savings because patients do not need to take an androgen antagonist to prevent the flare-up reaction that occurs with early use of GnRH analogues.

Additional economic questions remain to be answered, including the average cost per treatment course based on the duration of therapy and the costs of additional anticancer treatment or hospital care due to treatment failure or adverse effects of either GnRH analogues or antagonists. The lack of survival data in patients treated with degarelix also precludes the calculation of other cost-efficacy outcomes, such as cost per year of life gained. Further pharmacoeconomic analyses of degarelix are needed.

Future Directions

Additional clinical trials that are completed but not yet published or are currently under way seek to clarify the potential benefits of degarelix and its most effective dosing regimen. For example, a trial is assessing the tolerability and efficacy of degarelix given as depot injections of 240 mg (injectable solutions of 40 and 60 mg/mL) at months 1, 3, 6, and 9 after an initial starting dose, compared with the same 240-mg maintenance doses given at months 1, 4, 7, and 10; this study has reached its full enrollment.[41] To determine whether lower loading doses may provide benefit for prostate cancer patients, a study is being conducted to assess a 200-mg loading dose followed by either 60- or 80-mg monthly maintenance doses.[42] Other trials[43,44] are assessing the activity of higher maintenance doses of 360 and 480 mg given as subcutaneous solutions of 60 mg/mL at months 1, 4, 7, and 10 after a loading dose of 240 mg. Further studies are evaluating the utility of degarelix as second-line therapy after treatment failure with a GnRH analogue.[45,46]

The effects of degarelix beyond 1 year of therapy remain to be determined. To better define the longer-term effects of degarelix, an ongoing study is assessing its activity over a treatment period of up to 60 months.[47] Patients in this trial are receiving monthly degarelix maintenance doses of 160 mg (loading dose not available). Adverse effects of long-term therapy remain to be determined as well.

Other questions that remain unanswered concern the effects of degarelix on survival and quality of life and the optimal time to start treatment in patients who are diagnosed with prostate cancer. Another question is why some patients fail to respond to degarelix therapy. It may be valuable to investigate cellular characteristics and GnRH receptor structure, as well as PK properties and related gel formation, in

nonresponders. Finally, as stated earlier, the economic impact of degarelix remains to be studied as well.

Limitations of this review include the use of material published only in English as well as the potential for publication bias. Furthermore, although every effort was made to identify all pertinent studies involving degarelix in prostate cancer, the potential exists that the search methods may have limited the identification of additional information.

CONCLUSIONS

Prostate cancer is the most common cancer diagnosis among men in the United States. The decision to initiate treatment is based on the stage of the disease and life expectancy of the patient. Treatment options include surgery, radiation, chemotherapy, and medical androgen ablation. Hormonal therapy using GnRH analogues or androgen antagonists is commonly used to reduce the androgenic growth stimulus imparted on malignant prostate tissue. GnRH analogues have been a mainstay of therapy for many years because of their ability to reduce the synthesis and release of LH through desensitization of GnRH receptors on gonadotropic tissue. The decrease in LH causes a reduction in androgen synthesis in gonadal tissue. Although GnRH analogues are effective, drawbacks include the predictable flare-up reaction associated with increased androgen synthesis that occurs during the early stages of treatment and subsides within 2 to 3 weeks, as well as a delay in antitumor activity.

Degarelix is a potent synthetic GnRH antagonist that blocks the GnRH receptor on gonadotropic tissue, resulting in an immediate reduction in LH and testosterone synthesis. Because of the formation of a gel depot of drug after subcutaneous administration, degarelix has a PK profile akin to that of an agent with controlled-release properties; a degarelix loading dose of 240 mg SC and monthly maintenance doses of 80 mg result in a constant presence of drug that reduces testosterone concentrations to those achieved with surgical castration. In contrast to the GnRH analogues, degarelix does not cause any flare-up symptoms. Degarelix also lacks the symptomatic histamine release seen with other GnRH antagonists. Adverse effects are consistent with hormonal therapy and include a flushing reaction and injection-site discomfort. There are no known drug interactions with degarelix.

Additional clinical studies to observe the effects of degarelix in various dosing amounts and schedules are currently under way. Studies are also evaluating the potential benefit of degarelix as a second-line agent in patients who did not achieve adequate treatment outcomes with GnRH analogues.

In conclusion, degarelix is a viable treatment option for patients with prostate cancer. Mild adverse effects, favorable PK profile, and predictable clinical effects are important advantages. Pharmacoeconomic and quality-of-life studies should be performed to clarify the role of this agent in managing patients with prostate cancer.

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