Degarelix: a new hormonal treatment for prostate cancer

According to NICE, prostate cancer constitutes about 25% of new diagnoses of malignant cancer in men in England and Wales. The largest single area of spending on cancer drugs is on hormonal therapy, accounting for about 40% of the £292 million total. This article focuses on a novel hormonal treatment for prostate cancer, degarelix.

Prostate cancer is now the most frequently diagnosed cancer in European and American men. In the UK, prostate cancer accounts for around one-quarter of all new male cancer diagnoses and the incidence appears to be increasing. Prostate cancer incidence rates increase steeply with age. In Europe, prostate cancer mortality has increased by about 16% since 1995, largely as a result of the rapid rise in the ageing male population.

Prostatic epithelial cells depend on androgens for proliferation, differentiation and function, and the androgen, testosterone, is essential for prostatic tumour cell proliferation and survival. Most of the androgens originate from the testes (only around 5–10% are derived from adrenal biosynthesis). Testicular testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis (Figure 1). The hypothalamic gonadotrophin-releasing hormone (GnRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH), which stimulate testosterone release from the testes. Testosterone, in turn, stimulates prostate cancer cell proliferation via the action of its active metabolite, dihydrotestosterone, on androgen receptors in the prostate cells; circulating testosterone exerts a negative feedback control on hypothalamic LH secretion.

If prostate cells are deprived of androgenic stimulation, they undergo apoptosis. Thus suppression of androgen action forms the basis of androgen deprivation therapy (ADT). In advanced disease, the mainstay of treatment is ADT, which can provide effective palliation.

**Current therapy**

GnRH agonists act by stimulating the natural GnRH receptors in cells of the anterior pituitary gland. Constant exposure to such high-affinity stimulation in the therapeutic context results in downregulation of pituitary receptors, inhibition of FSH and LH release, and a concurrent reduction in testosterone production. Randomised trials suggest that, as a class, GnRH agonists are similar to orchidectomy for the treatment of metastatic prostate cancer, in terms of patient

![Figure 1. Regulation of testosterone secretion by the hypothalamic-pituitary-gonadal axis. GnRH, gonadotrophin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone.](image-url)
survival. For example, in a multi-centre, randomised trial in the UK and Ireland in patients with previously untreated metastatic prostate cancer, there was no difference in overall survival between the GnRH analogue, goserelin, and orchidectomy at a median follow-up of two years. However, while GnRH agonists have the desired clinical effect in terms of castration, they stimulate testosterone production before shutting it down. The initial testosterone surge can result in a transient increase (flare) in prostate cancer growth and in some patients can lead to a worsening of symptoms attributable to rapid cancer growth, such as bone pain and urinary obstruction, known as the flare phenomenon. For this reason, patients beginning GnRH agonist therapy are generally also treated with short-term (eg three weeks’ duration) oral anti-androgen therapy to prevent flare. However, it is less well known that patients may also experience additional surges in serum testosterone due to re-administration of GnRH agonists (acute-on-chronic flare response or microsurge); testosterone surges may also occur at any time during treatment (breakthrough response).12

Breakthrough increases of serum testosterone in medically castrated patients with prostate cancer could have clinical implications regarding prostate-specific antigen (PSA) progression. In one study, patients with breakthrough increases in testosterone of >32ng/dL had a significantly shorter survival free of androgen-independent progression than patients without these events (Figure 2). Conversely, there is evidence suggesting that intermittent ADT may offer equivalent efficacy to continuous ADT, and this may be a complex issue.

Moreover, several conventional GnRH agonists do not achieve castrate levels of testosterone (defined as ≤50ng/dL) in 1–12.5% of patients or fail to achieve levels comparable to orchidectomy (20ng/dL) in 13–40% of patients. Furthermore, serum levels of testosterone are rapidly reduced by orchidectomy with castrate levels of testosterone occurring after about 2.5 hours. In contrast, with GnRH agonists, castration is delayed, with lower testosterone levels only achieved 2–4 weeks after the initial injection.

**GnRH blockers**

GnRH blockers are a new class of hormonal agents that occupy GnRH receptor sites without activation, producing an immediate and pronounced suppression of testosterone without an initial surge. However, some GnRH antagonists have been associated with serious histamine-mediated side-effects due to excess histamine release from mast cells. Abarelix, the first antagonist to undergo clinical development, was associated with an increased risk of immediate-onset systemic allergic reactions and was withdrawn voluntarily in the USA in 2005.

**Degarelix**

Degarelix is a new GnRH blocker, due to be launched in the UK in 2009. This article reviews the properties of degarelix and the evidence supporting its use in patients with prostate cancer.

**Pharmacology/mode of action**

GnRH blockers, such as degarelix, inhibit the production of testosterone in men by directly and competitively blocking pituitary GnRH receptors. This blockade directly suppresses the secretion of LH and FSH and thereby reduces the production of testosterone by the testes.

Degarelix is the product of a targeted peptide development programme; its biochemical structure comprises a synthetic linear decapeptide amide modelled on normal human GnRH. During development, structural modifications were introduced with the aim of reducing the agent’s histamine-releasing potential, while maintaining or increasing drug

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**Figure 2.** Survival free of androgen-independent progression analysis according to serum testosterone behaviour in relation to lowest castrate threshold established at 32ng/dL. Group 1, patients with all three serum testosterone determinations <32ng/dL. Group 2, patients with breakthrough increases >32ng/dL.
potency. Moreover, degarelix is water-soluble and, upon subcutaneous (sc) administration, forms a unique gel-like depot without any additional vehicle being present. This results in a sustained release of the compound into the circulation, ensuring that a long-lasting clinical effect is maintained.

In animal studies, degarelix produced rapid, long-lasting and dose-dependent suppression of the pituitary gonadal axis as revealed by the decrease in plasma LH and testosterone levels. In a rat model of prostate cancer, degarelix suppressed testosterone to castrate levels within two days and maintained such levels throughout the study. This model, degarelix also showed similar control of tumour volume compared to surgical castration. In a study on rat peritoneal mast cells, degarelix displayed only weak histamine-releasing properties, and of the antagonists tested (Nal-Glu, cetrorelix, ganirelix, azalin B and abarelix), it possessed the lowest propensity to release histamine.

In healthy volunteers, degarelix rapidly reduces levels of LH, and there is a rapid reduction of testosterone to castrate levels. The half-life of degarelix is substantially longer after sc and intramuscular (im) administration than after intravenous (iv) injection, due to depot formation in body tissues (gel depot formation with iv administration was avoided by the use of microgram doses).

**Efficacy**

Two open-label, randomised, dose-finding phase II trials conducted in Europe and North America established the doses of degarelix to be used in phase III of clinical development. In the North American study, 127 patients received an initial dose of either 200 or 240mg followed by monthly maintenance doses of 80, 120 or 160mg. Both studies showed that degarelix induced fast, profound and sustained testosterone and PSA suppression in prostate cancer patients, without evidence of testosterone surge or clinical flare. From these studies, 240mg was established as the most effective induction dose of degarelix and 80 and 160mg as the most suitable maintenance doses. These doses were further investigated in the phase III setting.

**Phase III study**

A pivotal, randomised controlled phase III trial showed that degarelix (starting dose of 240mg and monthly maintenance doses of 80 or 160mg) was as effective as the GnRH agonist leuprolide (standard monthly 7.5mg dose) in maintaining low testosterone levels (0.5ng/mL) over a one-year treatment period. The trial involved 610 prostate cancer patients (any stage; median age 72 years) requiring ADT. Degarelix was administered by sc injection and leuprolide by im injection.

Both degarelix doses were as effective as leuprolide at inducing and sustaining testosterone suppression to castrate levels (0.5ng/mL) throughout the one-year study (Figure 3). The degarelix regimens of 240/80 and 240/160mg achieved a more rapid reduction of testosterone than leuprolide (Figure 4). Thus, with degarelix, median testosterone level was reduced by >90% by day three, compared with a 65% increase in the median testosterone level in the leuprolide group. Indeed, median testosterone levels in the leuprolide group were above castrate levels (>0.5ng/mL) until the measurements on day 28.

In the leuprolide group, the antiandrogen, bicalutamide, could be administered at the start of treatment for clinical flare protection at the discretion of the investigator. A surge in testosterone (defined as a testosterone increase of ≥15% from baseline, on any two days during the first two weeks) occurred in 81% of patients receiving leuprolide alone and in 74% of those receiving leuprolide plus antiandrogen (11% of all leuprolide patients received concomitant bicalutamide). Testosterone increases of >0.25ng/mL (microsurges) occurred in eight patients (4%) in the leuprolide group, with
testosterone breakthrough (>0.5 ng/mL) occurring in four of these patients (2%). Neither dosing schedule of degarelix induced testosterone surge or microsurge, both of which were seen with leuprolide.

The steady decrease in PSA levels in all treatment groups during the one-year study provided biochemical evidence of clinical response. However, degarelix was associated with a more rapid reduction in PSA levels than leuprolide (Figure 5). Degarelix reduced PSA levels at day 14 (by 64% with degarelix 240/80mg, 65% with degarelix 240/160mg) and day 28 (85% and 83%, respectively) to a significantly greater extent than leuprolide (reductions of 18% and 68% after 14 and 28 days, respectively; both \( p < 0.001 \)). PSA suppression was maintained throughout the study. Degarelix monotherapy also provided a similar PSA decrease to that achieved with leuprolide plus antiandrogen for flare protection.

In the pivotal phase III trial, there was a higher incidence of injection-site reactions with degarelix compared with leuprolide (40% versus <1%; \( p < 0.001 \), respectively), resulting in discontinuation in about 1% of the patients receiving degarelix. These reactions occurred predominantly after the first injection (33% of starting-dose injections versus 4% of maintenance-dose injections) and were mostly of mild-to-moderate intensity. The difference in incidence of injection-site reactions might be due to the different routes of administration (sc versus im) and the injection volume. Local injection-site reactions have previously been reported with GnRH agonists when given sc.30,31

**Tolerability**

In a worldwide clinical development programme that started in 1996, degarelix has been administered to over 2000 patients including patients with prostate cancer in two phase II and one phase III trials with no reported cases of immediate-onset systemic allergic reactions, to date. The most frequently reported side-effect associated with degarelix therapy is hot flushes, an expected androgen withdrawal symptom. Other common adverse events reported in these clinical trials of degarelix included fatigue, back pain, arthralgia and urinary tract infection.

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When administered in the clinic, degarelix forms a unique sustained-release depot that allows a steady and controlled release of the drug into the circulation and ensures a long-lasting clinical effect. Degarelix produces a rapid, profound and sustained reduction in serum testosterone and PSA without the initial stimulation seen with GnRH agonists such as leuprolide. Moreover, the absence of testosterone surge with degarelix allows degarelix monotherapy to achieve PSA suppression without the need for concomitant antiandrogen for flare protection. The absence of testosterone microsurges after repeated administration of degarelix may translate to longer-term benefits through effective testosterone control.13

Marketing authorisation for a degarelix 240mg starting dose and an

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**Figure 4.** Median serum testosterone during the first month of treatment with degarelix or leuprolide

[p=0.001 degarelix (both doses) versus leuprolide]
80mg monthly maintenance dose is expected in early 2009 from both European and US regulatory agencies. Further direct comparisons of degarelix and GnRH agonists in randomised controlled trials will establish the optimal approach to the long-term management of prostate cancer and the role of degarelix in treatment.

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References
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Figure 5. Median percentage change in PSA levels in patients treated with degarelix and leuprolide during the first two months of treatment.28