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Title:

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An update on the use of gonadotropin-releasing hormone antagonists in prostate cancer

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Abstract: Androgen deprivation therapy (ADT) is the main treatment approach in advanced prostate cancer and in recent years has primarily involved the use of gonadotropin-releasing hormone (GnRH) agonists. However, despite their efficacy, GnRH agonists have several drawbacks associated with their mode of action. These include an initial testosterone surge and testosterone microsurgs on repeat administration. GnRH antagonists provide an alternative approach to ADT with a more direct mode of action that involves immediate blockade of GnRH receptors. Antagonists produce a more rapid suppression of testosterone (and prostate-specific antigen [PSA]) without a testosterone surge or microsurgs and appear to offer an effective and well tolerated option for the hormonal treatment of prostate cancer. Comparisons with GnRH agonists have shown GnRH antagonists to be at least as effective in achieving and maintaining castrate testosterone levels in patients with prostate cancer. Furthermore, with antagonists, the lack of an initial testosterone surge (which may cause clinical flare) may allow more rapid relief of symptoms related to prostate cancer, avoid the need for concomitant antiandrogens to prevent clinical flare (so avoiding any antiandrogen-associated adverse events) and allow GnRH antagonist use in patients with high tumour burden and/or acute problems such as spinal cord compression. Although several antagonists have been investigated, only degarelix and abarelix are currently available for clinical use in prostate cancer. Currently, degarelix is the most extensively studied and widely available agent in this class. Degarelix is one of a newer generation of antagonists which, in a comprehensive and ongoing clinical development programme, has been shown to provide rapid, profound and sustained testosterone suppression without the systemic allergic reactions associated with earlier antagonists. This review examines the currently available data on GnRH antagonists in prostate cancer.

Keywords: abarelix, degarelix, GnRH agonist, GnRH antagonist, prostate cancer

Introduction

Around 70 years ago, Huggins and Hodges first demonstrated the responsiveness of metastatic prostate cancer (PCa) to androgen suppression [Huggins and Hodges, 1941]. Since then, androgen deprivation therapy (ADT) has formed the mainstay of treatment for advanced disease. ADT originally involved orchiectomy or estrogens; however, these modalities were superseded by gonadotropin-releasing hormone (GnRH) agonists. The agonists avoid the emotional and psychological effects of surgical castration and in recent decades have become the most common approach to ADT [Heidenreich *et al.* 2010].

However, these agents have drawbacks associated with their mode of action, including an initial testosterone surge, which can delay castration and may stimulate PCa cells, leading to an exacerbation of clinical symptoms (flare) [Thompson, 2001; Van Poppel and Nilsson, 2008]; agonists can also cause testosterone microsurgs on repeat administration.

More recently, a new approach to ADT has emerged in the form of GnRH antagonism. This involves direct and immediate blockade of GnRH receptors, preventing release of luteinizing hormone (LH) and follicle-stimulating

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hormone (FSH) and producing rapid suppression of testosterone without an initial surge. The first antagonist to undergo clinical development was abarelix, which was approved for clinical use in the USA at the end of 2003 [Mongiart-Artus and Teillac, 2004]. However, in response to reports of systemic allergic reactions, an extensive risk management programme was imposed and in 2005 abarelix was voluntarily withdrawn from the US market [Huhtaniemi *et al.* 2009]. The drug is still available in Germany for the initiation of medical castration in advanced or metastatic hormone-dependent PCa when androgen suppression is necessary [Kirby *et al.* 2009]. Launch of abarelix across Europe is planned following the approval of the drug in 11 additional European Union countries in August 2010 (see <http://www.specialityeuropeanpharma.com/sepproducts.html>).

More recently, degarelix, the first of a new generation of GnRH antagonists, has been developed for the treatment of PCa. In a comprehensive and ongoing clinical development programme, degarelix provided fast, profound and sustained testosterone suppression without the systemic allergic reactions associated with abarelix. Degarelix is indicated for the treatment of advanced hormone-dependent PCa and is currently approved for use in many countries in North and South America and Europe. This review will examine currently available data on GnRH antagonists in PCa.

Mechanism of action

GnRH antagonists induce castration by a different mechanism to that of GnRH agonists. Agonists produce intense initial stimulation of GnRH receptors, causing a marked rise in LH and FSH and, as a consequence, testosterone. Eventually, agonist-induced overstimulation overrides the natural pulsatile control of LH release, leading to receptor desensitization or downregulation, which suppresses LH and FSH secretion and reduces testosterone to castrate levels [Heidenreich *et al.* 2010]. In contrast, GnRH antagonists act more directly, competitively binding to and blocking pituitary GnRH receptors and causing an immediate blockade of LH and FSH secretion [Heidenreich *et al.* 2010; Van Poppel and Nilsson, 2008]. This produces rapid testosterone suppression, without any initial stimulation or surge.

Animal studies show not only that GnRH antagonist administration suppresses LH and testosterone to castrate levels but also that administration of a GnRH antagonist before an agonist will blunt the characteristic agonist-induced LH and testosterone surge (Figure 1) [Pinski *et al.* 1992; Sharma *et al.* 1992]. However, after the antagonist is removed, there is an increase in testosterone and LH, presumably agonist driven, to above castration levels. Although the increase is more modest than that with agonist alone, it appears to be more prolonged. Thus agonist-induced testosterone suppression appears to require at least some level of receptor activation to induce downregulation, and thus some degree of initial testosterone induction is likely – it appears that the agonist-induced testosterone surge may be blunted but not eliminated by prior administration of an antagonist.

Abarelix

Clinical efficacy

A phase II open-label trial in 242 patients with PCa requiring initial hormonal treatment compared the efficacy of abarelix ($n=209$) with that of GnRH agonists ($n=33$) \pm antiandrogen. Abarelix 100 mg was administered intramuscularly on days 1 and 15 followed by 50 mg on day 29 and every 28 days thereafter; results were reported only up to day 27 [Tomera *et al.* 2001]. Phase III studies included two US trials and a European trial. In a 3-month US trial, 269 men with locally advanced and metastatic disease were randomized to abarelix 100 mg ($n=180$) or leuprolide 7.5 mg ($n=89$) monthly; the abarelix group received an additional injection on day 15 [McLeod *et al.* 2001]. In the second US trial, 255 patients with stage D1/D2 disease were randomized to abarelix 100 mg monthly ($n=170$) or leuprolide 7.5 mg monthly and bicalutamide 50 mg daily ($n=85$) over 24 weeks [Trachtenberg *et al.* 2002]. In the European phase III trial, 177 patients with advanced or metastatic cancer were treated for 48 weeks with abarelix 100 mg 4-weekly or goserelin 3.6 mg 4-weekly plus bicalutamide 50 mg daily [Selvaggi *et al.* 2001].

In phase II/III trials, abarelix effectively suppressed testosterone to castrate levels in patients with PCa but did not cause an associated testosterone surge. After 27–29 days, castration was achieved in $\geq 93\%$ of patients receiving abarelix [Trachtenberg *et al.* 2002; McLeod *et al.* 2001];

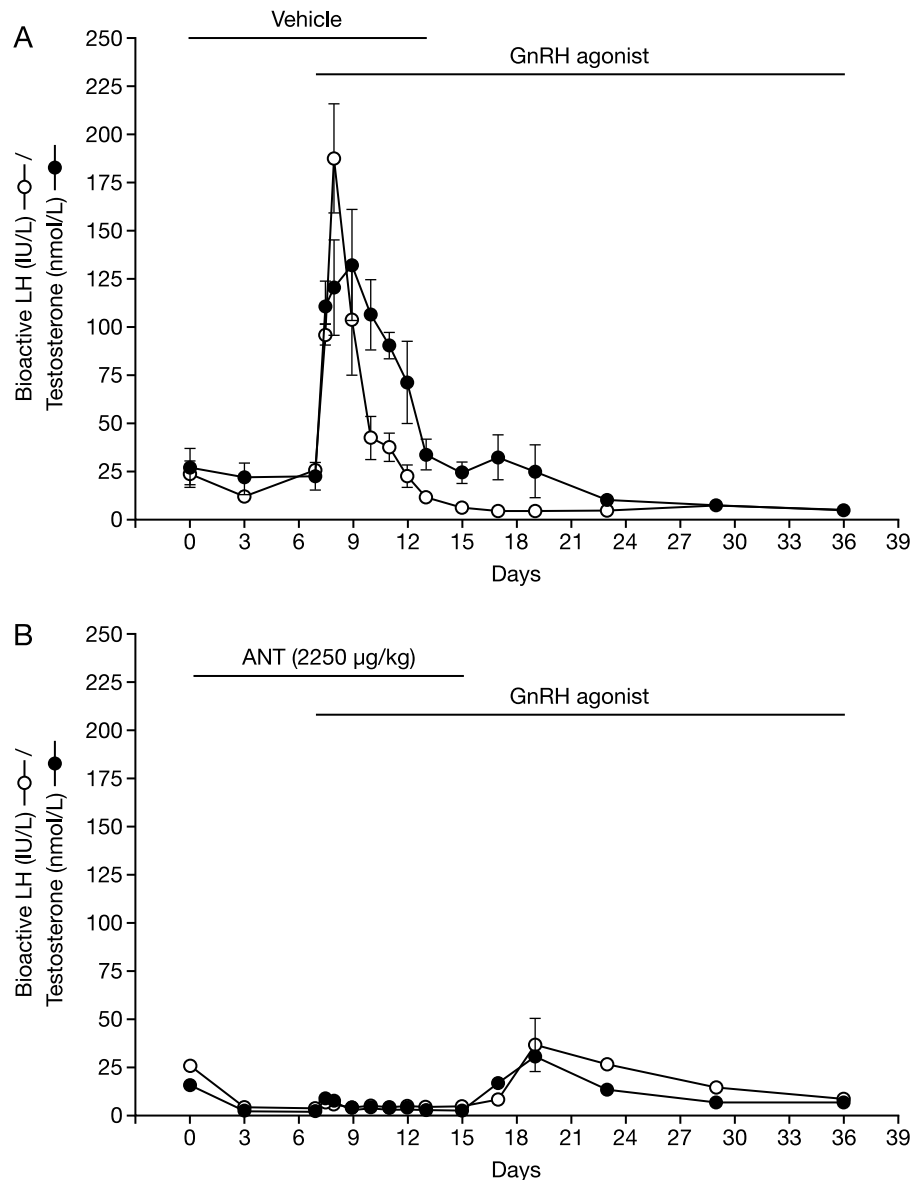


Figure 1. Mean (\pm SE) of serum bioactive luteinizing hormone (LH; open circles) and testosterone (filled circles) of adult male monkeys (five per group) receiving an implant loaded with the gonadotropin (GnRH) agonist (buserelin) on day 7. On days 0–15 animals were treated, in addition to the GnRH agonist, with GnRH antagonist vehicle (upper panel) or Nal-Glu GnRH antagonist at a dose of 2250 μ g/kg daily (bottom panel). ANT, antagonist. [Reproduced with permission from Sharma *et al.* [1992]].

Selvaggi *et al.* 2001; Tomera *et al.* 2001]. Abarelix was as effective in achieving castration as GnRH agonists \pm antiandrogens but was associated with a more rapid suppression of testosterone [Tomera *et al.* 2001]. A US phase III trial ($n=269$) showed that in men who had achieved castration by day 29, castration was maintained in 98.8% of the abarelix group and 97.7% of the leuprolide group [McLeod *et al.* 2001]. In the European phase III trial ($n=177$), castration was achieved

by day 84 in 99% of patients receiving abarelix and 100% of those receiving goserelin/bicalutamide [Selvaggi *et al.* 2001].

Prostate-specific antigen (PSA) reductions during phase III trials were similar for abarelix and GnRH agonists \pm antiandrogen, although in two trials this was initially more rapid with abarelix [Mongiart-Artus and Teillac, 2004; McLeod *et al.* 2001]. Abarelix was associated with rapid

decreases in LH and FSH levels in US phase III trials [Trachtenberg *et al.* 2002; McLeod *et al.* 2001].

Long-term clinical efficacy

In a US phase III trial, long-term ability to achieve and maintain castration was maintained at 24 weeks in a similar proportion of abarelix- and GnRH agonist/antiandrogen-treated patients (90.4% *vs.* 83.8% of patients, respectively) [Trachtenberg *et al.* 2002]. However, based on data from two randomized, open-label, active-comparator trials, the abarelix package insert warned that effectiveness of testosterone suppression decreases with continued dosing in some patients and that effectiveness beyond 12 months had not been established (see <http://www.druglib.com/druginfo/plenaxis>). Indeed, waning of castration rates after 24 weeks appeared to occur more frequently with abarelix than active controls [Mongiart-Artus and Teillac, 2004]. In the phase III European trial, escape from castration was more common with abarelix (22%) than agonist/antiandrogen (8%) and time to escape was significantly shorter with abarelix ($p = 0.007$) [Debruyne *et al.* 2006].

Safety

In phase III studies, abarelix displayed a safety profile generally comparable to that of leuprolide \pm bicalutamide [Debruyne *et al.* 2006; Trachtenberg *et al.* 2002; McLeod *et al.* 2001]. However, allergic reactions were a major concern with abarelix [Mongiart-Artus and Teillac 2004]. Overall, immediate-onset systemic allergic reactions were observed in 15/1397 (1.1%) patients with PCa (mostly in men without advanced symptomatic disease) who received abarelix [Mongiart-Artus and Teillac, 2004]. The cumulative risk of these reactions increased with duration of treatment. Furthermore, in a trial involving patients with advanced symptomatic PCa, 3.7% of patients experienced immediate-onset systemic allergic reactions (see <http://www.druglib.com/druginfo/plenaxis>).

Degarelix

Degarelix is a third-generation GnRH antagonist synthetically modified with a view to reducing the histamine-releasing activity associated with previous GnRH antagonists.

Preclinical studies

In preclinical studies, degarelix demonstrated a fast and sustained dose-dependent and reversible suppression of the pituitary-gonadal axis, manifested by decreases in LH and testosterone levels, with a longer duration of action than other antagonists [Broqua *et al.* 2002]. Degarelix also inhibited tumour growth to a similar extent to surgical castration [Principalle *et al.* 2007]. In animal studies [Broqua *et al.* 2002] and an *ex vivo* human skin model [Koechling *et al.* 2010], degarelix displayed only weak histamine-releasing properties, having the lowest propensity for histamine release among the GnRH antagonists tested.

Pharmacokinetics

Pharmacokinetic analysis indicates that upon subcutaneous administration degarelix forms a depot from which the drug distributes to the rest of the body [Steinberg, 2009]. In rats, degarelix release from the depot was characterized by a short initial burst followed by plasma concentrations decaying with a half-life of several weeks [White *et al.* 2007].

Following subcutaneous administration of degarelix 240 mg to PCa patients in the phase III trial (CS21), $AUC_{0-28 \text{ days}}$ was 635 ng/day per ml and C_{\max} was 66.0 ng/ml and occurred at $t_{\max} = 40$ h. Degarelix is eliminated biphasically, with a median terminal half-life of ~ 43 days for the starting dose and 28 days for the maintenance dose.

Clinical efficacy

Long-term phase II dose-finding trials. The efficacy and safety of degarelix has been evaluated in two randomized, 1-year dose-finding trials in Europe/South Africa [Van Poppel *et al.* 2008] and North America [Gittelman *et al.* 2008]. Degarelix produced fast, profound and sustained suppression of testosterone and PSA, with no evidence of a testosterone surge or systemic allergic reactions. The most effective starting dose was 240 mg and the most suitable maintenance doses were 80 mg and 160 mg; these doses were investigated further in a large phase III trial.

Phase III efficacy trial (CS21). The efficacy of degarelix was compared with the GnRH agonist leuprolide in a pivotal 1-year randomized phase III trial (CS21) in patients with histologically

confirmed PCa (all stages) for whom ADT was indicated [Klotz *et al.* 2008]. Patients ($n=610$) received degarelix 240 mg for 1 month followed by monthly doses of 80 mg ($n=207$) or 160 mg ($n=202$), or leuprolide 7.5 mg/month ($n=201$) for 1 year. Concomitant antiandrogen was available as flare protection in the leuprolide group at the investigator's discretion.

Both degarelix doses were as effective as leuprolide at reducing serum testosterone throughout the trial. Treatment response (testosterone suppression ≤ 0.5 ng/ml between 28 and 364 days) was achieved by similar proportions of patients in all three groups: 96.4–98.3% (intention-to-treat population). Degarelix was significantly faster than leuprolide at suppressing testosterone and PSA. By day 3, testosterone levels ≤ 0.5 ng/ml were achieved by 96.1% in the degarelix 240/80 groups compared with 0% in the leuprolide group [Klotz *et al.* 2008]; by day 14 these values were 100 and 18.2%, respectively (Figure 2) [Boccon-Gibod *et al.* 2008]. Testosterone surge (increase of $\geq 15\%$ from baseline on any 2 days during the first 2 weeks of treatment) was reported in 80% of patients receiving leuprolide *versus* 0% of those receiving degarelix. Eight patients (4%) receiving leuprolide had testosterone microsurges (increases of >0.25 ng/ml) in the week following the ninth injection; no testosterone microsurges were detected with degarelix [Klotz *et al.* 2008].

PSA was also suppressed more rapidly with degarelix: by day 14, median PSA had fallen by

64% and 65% in the 240/80 and 240/160 groups, respectively, compared with 18% for leuprolide; by day 28 these values were 85%, 83% and 68%. Degarelix also rapidly reduced median LH and FSH levels, which remained suppressed until the end of the trial. With leuprolide, however, there was an initial increase in LH and FSH, and FSH levels did not fall to the same extent as in the degarelix arms [Klotz *et al.* 2008].

Secondary endpoints from phase III efficacy trial

Prostate-specific antigen. Analyses of PSA data from the CS21 trial showed a significantly lower risk of PSA failure or death for patients receiving degarelix 240/80 mg compared with leuprolide 7.5 mg ($p=0.05$; log-rank) during the first year of treatment. PSA failure occurred mainly in patients with advanced disease and exclusively in those with baseline PSA >20 ng/ml [Tombal *et al.* 2010].

Patients with baseline PSA >20 ng/ml showed a significantly longer time to PSA failure with degarelix ($p=0.04$; log-rank) [Tombal *et al.* 2010]. In patients with baseline PSA >50 ng/ml, 29.2% of those receiving degarelix and 40.0% of those receiving leuprolide experienced PSA failure (the difference was not statistically significant; $p=0.10$).

In patients with metastatic disease, 21.6% of those in the degarelix 240/80 mg group and 36.2% of those in the leuprolide group experienced PSA failure (the difference was not statistically significant; $p=0.156$). An initial increase

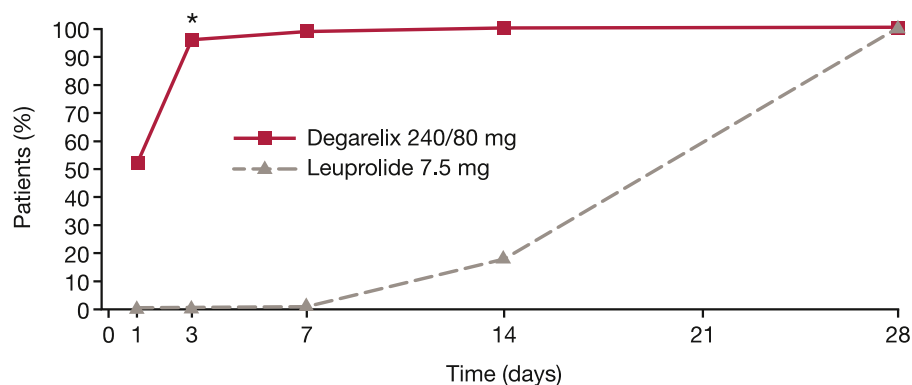


Figure 2. Percentage of patients with testosterone ≤ 0.5 ng/ml during the first month of treatment in the phase III comparative study CS21.

* $p < 0.001$ *versus* leuprolide (pairwise comparisons by Fisher's exact test) [Adapted from Persson *et al.* 2009].

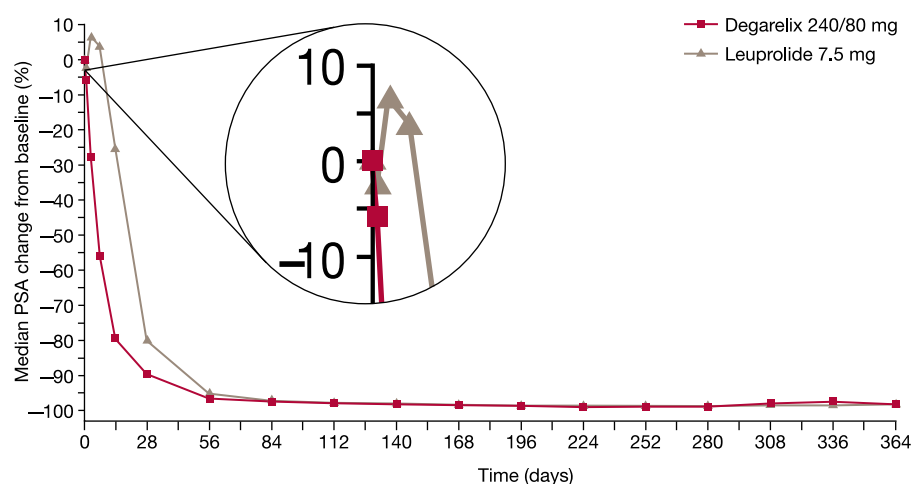


Figure 3. Median percentage change in prostate-specific antigen (PSA) from baseline for degarelix 240/80 mg versus leuprolide.

in PSA observed in patients with metastatic disease receiving leuprolide was not seen in the degarelix group [Tombal *et al.* 2010] (Figure 3). In the locally advanced subgroup, the proportion of patients with PSA failure was similar between treatment groups.

Overall, the proportion of patients achieving PSA < 4 ng/ml over time was similar in both groups, although this was achieved more rapidly with degarelix. PSA suppression < 4 ng/ml at day 28 was achieved by 59% of patients receiving degarelix versus 34% receiving leuprolide ($p < 0.0001$). Corresponding proportions at day 364 were 83% and 78% (difference not statistically significant; $p = 0.339$). For patients with metastatic disease, a higher proportion of those receiving degarelix achieved PSA < 4 ng/ml over the study period [Tombal *et al.* 2010].

Overall, these results may suggest the hypothesis that degarelix at 240/80 mg offers improved PSA control compared with leuprolide.

Serum alkaline phosphatase. Elevated levels of the bone markers serum alkaline phosphatase (S-ALP) and bone-specific alkaline phosphatase have been associated with progression of skeletal metastases in PCa [Lein *et al.* 2007; Lorente *et al.* 1996] and are significant predictors of early death [Robinson *et al.* 2008; Johansen *et al.* 2007; Ramankulov *et al.* 2007; Jung *et al.* 2004].

In CS21, S-ALP levels in both treatment groups were maintained around baseline in patients with localized and locally advanced disease [Schröder *et al.* 2010]. In patients with metastatic disease, baseline S-ALP levels were high, reflecting the presence of skeletal metastases. In this cohort, after initial peaks in both groups, S-ALP was suppressed by both treatments, falling below baseline by day 56 with degarelix 240/80 mg and by day 84 with leuprolide. At day 364, reduction in S-ALP was significantly greater with degarelix 240/80 mg than with leuprolide (mean S-ALP at day 364: leuprolide 179 IU/l, degarelix 96 IU/l, $p = 0.014$). In metastatic disease, the late rise in S-ALP levels seen during leuprolide treatment, which might suggest therapy failure, was not apparent with degarelix.

Analysis by baseline PSA showed S-ALP levels 3–4 times higher in patients with baseline PSA ≥ 50 ng/ml versus < 50 ng/ml. After initial peaks in both groups, patients with baseline PSA ≥ 50 ng/ml had greater absolute reductions in S-ALP and reductions from baseline with degarelix 240/80 mg than with leuprolide. Furthermore, there was a late rise in S-ALP with leuprolide (returning to baseline levels before the trial end), which was not observed with degarelix (S-ALP levels remained below baseline at trial end).

In patients with baseline PSA ≥ 50 ng/ml, the difference in suppression at day 364 between degarelix and leuprolide was statistically significant (83 vs. 163 IU/l; $p = 0.007$). In patients with

PSA < 50 ng/ml, S-ALP was maintained around baseline levels, irrespective of treatment.

These results may allow the generation of a hypothesis that suggests better S-ALP control and prolonged control of skeletal metastases with degarelix compared with the GnRH agonist leuprolide over a 1-year treatment period.

Effect of concomitant antiandrogen therapy. In CS21, 11% of patients (23/201) in the leuprolide group received concomitant bicalutamide for flare protection. A testosterone surge occurred in 81% of patients (144/178) receiving leuprolide without bicalutamide compared with 74% (17/23) of those receiving leuprolide and bicalutamide [Klotz *et al.* 2008].

PSA reduction from baseline was more rapid in patients receiving leuprolide/bicalutamide than in those receiving leuprolide alone. Thus, for patients starting antiandrogen therapy on/before day 7, median PSA was reduced by 61.7% on day 14 and 89.1% on day 28, compared with reductions of 15.3% and 61.7%, respectively, for patients not on antiandrogens. Indeed, PSA reduction from baseline in patients receiving leuprolide/bicalutamide was similar to that with degarelix [Klotz *et al.* 2008]. In patients with metastatic disease, there was an initial PSA surge in patients receiving leuprolide without concomitant antiandrogens; a smaller PSA surge was noted in leuprolide patients who were receiving

concomitant antiandrogens (Ferring, data on file) (Figure 4). No PSA surge was observed with degarelix 240/80 mg in the metastatic patient cohort.

The probability of testosterone ≤ 0.5 ng/ml from day 28 to day 364 (intention-to-treat analysis) was similar among patients who received no antiandrogen therapy (96.5%) and those starting antiandrogens on/before day 7 (95%) (Ferring, data on file).

Thus, since addition of an antiandrogen to a GnRH agonist does not always prevent testosterone surge, a GnRH antagonist may be a more reliable approach to surge and, as a consequence, flare protection.

Effect of baseline body weight on efficacy. During CS21, patients were stratified by body weight (<90 kg and ≥ 90 kg). Of 620 patients randomized to treatment, the majority (501/620) were < 90 kg. There were no discernable trends among patients receiving degarelix 240/80 mg indicating an effect of body weight on any of the following efficacy endpoints: the proportion of patients with testosterone ≤ 0.5 ng/ml from day 28 to day 364; the proportion of patients with testosterone ≤ 0.5 ng/ml on day 3; the proportion of patients with testosterone surge during the first 2 weeks of treatment; and the percentage change in PSA from baseline to day 14 and to day 28 (Ferring, data on file). Thus, no dose adjustments are required for

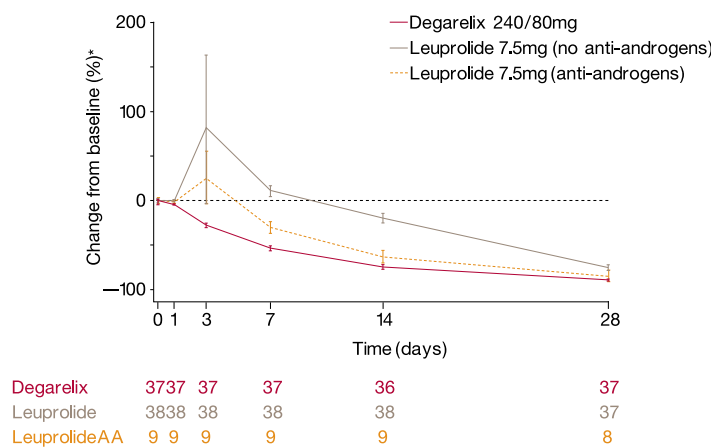


Figure 4. Mean (\pm standard error) percentage change in prostate-specific antigen from baseline during the first 28 days of treatment in patients with metastatic disease receiving degarelix 240/80 mg and in those who received leuprolide with or without antiandrogens (AA) in the phase III CS21 trial.

heavier patients (i.e. body weight ≥ 90 kg) receiving degarelix 240/80 mg.

Long-term extension of phase III clinical trial. Patients completing CS21 were eligible to enter an ongoing 5-year extension study (CS21A) of safety and efficacy in patients continuing on degarelix or crossing over from leuprolide to degarelix after 1 year [Persson *et al.* 2010; Plekhanov *et al.* 2010]. Patients initially receiving degarelix continued with the same monthly maintenance dose (160 mg or 80 mg), while those previously receiving leuprolide 7.5 mg were randomized to a starting dose of degarelix 240 mg followed by monthly maintenance doses of 80 mg or 160 mg.

Beyond 1 year, the risk of PSA failure or death decreased in patients switched from leuprolide to degarelix. At a median follow up of 27.5 months, there was a significant improvement in PSA progression-free survival hazard rates from 0.20 events/year in the first year to 0.08 events/year following switch in the leuprolide/degarelix group ($p=0.003$); corresponding hazard rates for the continuous degarelix 240/80 mg group were 0.11 and 0.14 events/year (difference not statistically significant; $p=0.464$), demonstrating a consistent effect of degarelix over time. The same pattern of hazard change was observed in the subgroup of patients with baseline PSA levels >20 ng/ml. After a median follow up of 27.5 months, PSA progression-free survival hazard rates improved from 0.38 events/year in the first year to 0.19 events/year following the switch to degarelix in leuprolide patients ($p=0.031$); corresponding hazard rates for degarelix were 0.23 and 0.23 events/year (difference not statistically significant; $p=0.988$) [Plekhanov *et al.* 2010].

The time for 25% of patients with baseline PSA >20 ng/ml to experience PSA failure or death ($TTP_{25\%}$) was numerically longer with degarelix than leuprolide (407 *vs.* 303 days; difference not statistically significant, $p=0.085$) over 1 year. An even greater difference was seen when analysing $TTP_{25\%}$ using degarelix data beyond 1 year: 514 *versus* 303 days ($p=0.01$) for degarelix *versus* leuprolide [Plekhanov *et al.* 2010] (Figure 5).

Comparison of degarelix with abarelix. Although there are no trials directly comparing the GnRH antagonists abarelix and degarelix,

indirect comparisons between studies suggest that achievement of castration with degarelix may be more rapid than with abarelix [European Medicines Agency, 2010; Trachtenberg *et al.* 2002; McLeod, *et al.* 2001].

Safety

Overall safety. Degarelix was well tolerated during its clinical development programme. In the 1-year phase II and III studies, most adverse events were related to androgen deprivation (i.e. hot flushes, weight increase, etc.). The most frequent adverse events were hot flushes, injection-site pain, and fatigue [Gittelman *et al.* 2008; Klotz *et al.* 2008; Van Poppel *et al.* 2008]. Most events were mild to moderate in intensity; there were no dose-dependent side effects or systemic allergic reactions.

In the 1-year phase III study [Klotz *et al.* 2008], both degarelix 240/80 mg or 240/160 mg and leuprolide had a similar incidence of adverse events. As in phase II studies, there were no systemic allergic reactions with degarelix. Degarelix was associated with a higher rate of injection-site reactions than leuprolide (40% in pooled degarelix arms *vs.* $<1\%$, respectively, $p<0.001$), although these occurred predominantly after the first injection and were mostly mild or moderate. Moreover, the difference in injection-site reaction rates may reflect different routes of administration (subcutaneous with degarelix *vs.* intramuscular with leuprolide) and injection volume. Local injection-site reactions have also been noted with GnRH agonists when administered subcutaneously (see <http://products.sanofi-aventis.us/eligard/eligard.pdf>) [Oka *et al.* 2006]. While there was also a higher incidence of chills reported with degarelix, there was a significantly lower incidence of musculoskeletal events (arthralgia) and urinary tract infections with degarelix than leuprolide. In total, five patients (2%) died in each of the degarelix groups, compared with nine (4%) in the leuprolide group; none of the deaths were considered to be related to the study drugs.

Musculoskeletal adverse events.

Musculoskeletal adverse events were reported in 17% *versus* 26% ($p=0.001$) of patients in the degarelix and leuprolide groups, respectively, during the 1-year phase III trial [Crawford *et al.* 2010a]. Results from the long-term extension

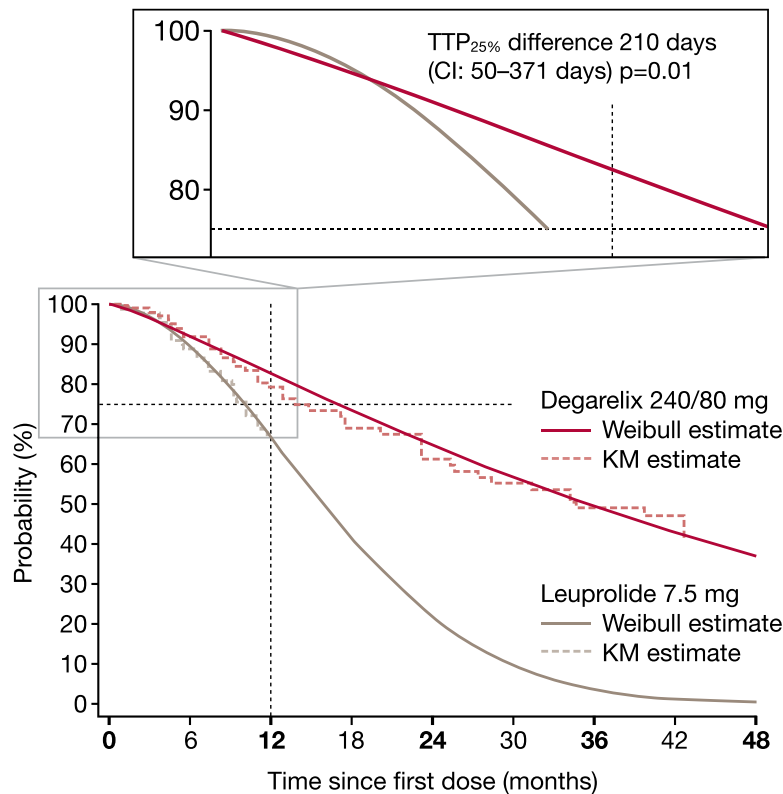


Figure 5. The probability of freedom from prostate-specific antigen (PSA) failure or death over time for patients with baseline PSA ≥ 20 ng/ml in the CS21 and CS21a trials. The magnified area of the graph shows the time for 25% of patients with baseline PSA ≥ 20 ng/ml to experience PSA failure or death (TTP_{25%}).

study (CS21A) showed that beyond 1 year, the musculoskeletal event rate was similar between patients continuing on degarelix (16%) and those switching from leuprolide to degarelix (18%, difference not statistically significant, $p=0.75$) [Crawford *et al.* 2010b]. These observations suggest a lower incidence of musculoskeletal adverse events with degarelix than with leuprolide.

The significantly lower musculoskeletal adverse event rate with degarelix during CS21 and the improved musculoskeletal adverse event rate for those switching to degarelix during CS21A, together with the better S-ALP control than leuprolide in patients with metastatic disease [Schroder *et al.* 2010] support the hypothesis that degarelix may further prolong control of skeletal metastases compared with GnRH agonists during long-term treatment.

Cardiovascular safety. A recent analysis evaluated the comparative cardiovascular safety of degarelix 240/80 mg or 240/160 mg and

leuprolide in the phase III CS21 trial [Smith *et al.* 2010]. Outcomes included QT interval and cardiovascular adverse events. Overall, degarelix and leuprolide displayed similar cardiovascular safety profiles. There were no significant differences between treatment groups for mean change in Fridericia's correction of QT (QTcF) during the trial. Marked prolongation of the QTc interval was uncommon ($\leq 1\%$) with either agent. There were no significant differences in rates of new ischaemic heart disease or arrhythmias. Supraventricular arrhythmias were the most common type of arrhythmia (pooled degarelix group 2%, leuprolide 4%). Other arrhythmias occurred in $\leq 1\%$ of patients in each group. The most frequently reported cardiac disorder was ischaemic heart disease (occurring in 4% of patients treated with degarelix and 10% of those on leuprolide).

Recently, the US Food and Drug Administration required manufacturers of GnRH agonists to include new safety warnings on their labels

regarding the increased risk of diabetes and certain cardiovascular diseases [US Food and Drug Administration, 2010]. In contrast, most (but not all) studies have reported that orchiectomy is not associated with greater risk of cardiovascular events [Levine *et al.* 2010; Alibhai *et al.* 2009; Keating *et al.* 2006]. These observations raise the possibility that cardiovascular risk may vary for different forms of ADT.

Additional analyses of men treated with degarelix showed a greater risk of cardiovascular events was associated with established cardiovascular disease; risk was also influenced by modifiable risk factors (e.g. obesity and alcohol consumption) but not variation in degarelix doses or testosterone values [Klotz *et al.* 2010]. This appears to suggest that the cardiovascular risk in patients treated with degarelix may be driven by normal aging.

Ongoing trials

The currently available data on the use of degarelix in advanced PCa, including evidence of the lack of clinical flare and subsequent testosterone microsurgs, has led to interest in its potential use in a number of additional clinical settings, which are being investigated in several ongoing clinical trials. These include: comparison of the safety and efficacy of degarelix given intermittently *versus* continuous ADT with leuprolide or degarelix in patients with PCa with prior treatment failure after localized treatment (CS37; ClinicalTrials.gov identifier: NCT00928434); comparison of degarelix with goserelin/bicalutamide, in terms of prostate size reduction, in patients of intermediate to high risk who require neoadjuvant hormone therapy before radiotherapy (curative intent) (CS30; ClinicalTrials.gov identifier: NCT00833248); comparison of degarelix with goserelin/bicalutamide, in terms of prostate volume reduction, in patients who are candidates for medical castration (CS31; ClinicalTrials.gov identifier: NCT00884273); comparison of the efficacy and safety of degarelix 3-month depot with goserelin in patients requiring ADT (CS35; ClinicalTrials.gov identifier: NCT00946920); an uncontrolled trial of degarelix as intermittent androgen deprivation for ≥ 1 cycle (CS29; ClinicalTrials.gov identifier: NCT00801242); an uncontrolled, exploratory trial of degarelix as second-line hormonal treatment after PSA failure in GnRH agonist-treated

patients with PCa (CS27; ClinicalTrials.gov identifier: NCT00738673). The results of these studies should help to provide invaluable data on the efficacy, safety and quality of life associated with degarelix use in a variety of therapeutic settings in PCa.

Other GnRH antagonists

Other GnRH antagonists, primarily in the early stages of development, have been investigated in PCa over the years [Huirne *et al.* 2001] but only degarelix and abarelix are available for clinical use.

Cetrorelix is used to prevent premature ovulation in controlled ovarian stimulation before assisted reproductive technologies (see <http://www.merckserono.com/en/products/fertility/infertility/cetrotide/cetrotide.html>); however, development in PCa has been discontinued. In prostate tumour xenografts in a nude mouse model, final volume and weight of tumours were significantly reduced after 8 weeks' treatment with cetrorelix [Lamharzi *et al.* 1998]. Cetrorelix also inhibited growth of an androgen-independent PCa cell line *in vivo* [Jungwirth *et al.* 1997]. Primary cell cultures from human PCa showed a reduction in cell growth rate and increase in DNA-fragmented cell number with cetrorelix [Castellón *et al.* 2006]. Several phase I/II studies were conducted with cetrorelix in patients with advanced PCa [Reissman *et al.* 2000; Gonzalez-Barcena *et al.* 1995, 1994]. In one study, after 6 weeks cetrorelix had reduced testosterone to castrate levels with a significant decrease in bone pain, relief in urinary outflow obstruction, and reversal of the signs of prostatism [Gonzalez-Barcena *et al.* 1994]. In patients with advanced PCa and metastases in the spinal cord, neurological symptoms regressed and bladder function improved after 3 months of cetrorelix treatment [Gonzalez-Barcena *et al.* 1995].

The GnRH antagonist acyline has been studied in humans [Amory *et al.* 2009; Page *et al.* 2006; Herbst *et al.* 2004, 2002] and is currently in phase I development for oncology (see <http://www.merriumpharma.com/content/portfolio/pipeline.asp>). After subcutaneous injection in healthy volunteers, acyline produces a rapid and sustained suppression of testosterone that can persist for up to 2 weeks [Herbst *et al.* 2004]. Recently, oral administration of acyline in a proprietary formulation (GIPET;

GI enhancing permeability technology) that enhances the oral bioavailability of peptides significantly suppressed testosterone and gonadotropins in volunteers, without untoward side effects, and was speculated as possibly having utility in the management of PCa [Amory *et al.* 2009].

Preliminary phase II data with teverelix (in phase II development for PCa) appeared to show suppression of testosterone to castrate levels [Reuters, 2008] although these data are not yet available in a peer-reviewed publication.

Ozarelix is in phase II development for the treatment of PCa (see http://www.sppirx.com/drugs_proprietary.html). It is associated with immediate and complete *in vivo* testosterone suppression, without the risk of surge/flare [Festuccia *et al.* 2010]. Ozarelix showed antiproliferative effects and produced an accumulation of cells in G2/M cell cycle phase in an *in vitro* study of two androgen-independent PCa cell models that are unresponsive to androgen stimulation [Festuccia *et al.* 2010]. The authors considered that their results may suggest that GnRH antagonists might have an anticancer effect in androgen-independent prostate models.

Summary

The pharmacological profile of GnRH antagonists – fast suppression of testosterone and PSA in the absence of the testosterone surge/flare associated with agonists – provides a promising new treatment option for PCa. Although several antagonists have been investigated in recent years, only degarelix and abarelix are currently available for clinical use in PCa. Moreover, abarelix has been associated with the risk of systemic allergic reactions and, although currently available in Germany, was withdrawn in the US in 2005 [Huhtaniemi *et al.* 2009]. By contrast, degarelix, the first of a new generation of GnRH antagonists, has been shown in an extensive clinical development programme to retain the efficacy benefits of these agents without the systemic allergic reactions associated with the earlier members of the class.

Clinical comparisons with GnRH agonists, the current standard of care in advanced PCa, show that GnRH antagonists, such as degarelix, are at least as effective in achieving and maintaining castrate testosterone levels in patients with PCa.

The absence of a testosterone surge with antagonists avoids initial stimulation of the cancer and worsening of clinical status, and allows more rapid relief of symptoms related to PCa. Because of this, concomitant antiandrogens are not required to prevent clinical flare during antagonist therapy, thereby avoiding antiandrogen-associated adverse events. In addition, the absence of the risk of clinical flare allows GnRH antagonist use in patients with high tumour burden and/or acute problems such as spinal cord compression.

In addition to the significantly faster suppression of testosterone and PSA with the antagonist degarelix than with the agonist leuprolide, degarelix also appears to offer better disease control during the first treatment year (fewer PSA failures, a significantly lower risk of PSA failure or death, lower S-ALP levels and fewer musculoskeletal adverse events). Furthermore, Initial longer-term data suggest that these benefits extend beyond 1 year, supporting the use of degarelix as first-line ADT. The full results from the ongoing extension study are awaited to help clarify the long-term safety and efficacy of degarelix. Although switching from an agonist to an antagonist appears to offer clinical benefits, preclinical data appear to suggest that switching from an antagonist to an agonist is still likely to be accompanied by a testosterone surge and its associated negative clinical implications.

The fast onset of action and lack of testosterone surge with the antagonist degarelix may be beneficial in a range of other clinical settings, such as neoadjuvant to radiation therapy and intermittent ADT, both of which are under investigation. Data from ongoing studies of degarelix in these and other clinical settings may help clarify those PCa patients most likely to benefit from the use of GnRH antagonists.

Conclusion

GnRH antagonists represent a pharmacological method of castration for patients with PCa that offers a more direct and logical mechanism of action than GnRH agonists. With their faster onset of testosterone suppression and absence of surge/flare, these agents appear to offer an effective and well tolerated alternative for the hormonal treatment of PCa. Currently, degarelix is the most extensively studied and widely available agent in this class.

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Conflict of interest statement

Professor Boccon-Gibod is an advisor to Ferring Pharmaceuticals. Egbert van der Meulen and Bo-Eric Persson are employees of Ferring Pharmaceuticals.

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