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Efficacy and safety of androgen deprivation therapy after switching from monthly leuprolide to monthly degarelix in patients with prostate cancer

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SUMMARY

Objectives: To evaluate whether switching prostate cancer (PCa) patients from leuprolide to degarelix is associated with any change in the efficacy of testosterone suppression or safety profile during the first 3 months. **Methods:** Participants were 134 patients with histologically confirmed PCa who had completed 1 year of treatment with leuprolide 7.5 mg monthly before being switched to degarelix. These patients were re-randomised for the extension trial to receive a starting dose of 240 mg degarelix followed by monthly maintenance doses of either 80 (n = 69) or 160 mg (n = 65). For efficacy assessment, serum testosterone, prostate-specific antigen (PSA), luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels measured at days 3, 7, 14, 28, 56 and 84 assessed whether treatment efficacy is sustained. Safety and tolerability assessments included adverse events (AEs), physical examinations, electrocardiograms and clinically significant changes in laboratory safety parameters. **Results:** Serum testosterone, LH, and PSA levels were all sustained in both treatment arms during the observation period. Interestingly, FSH levels were further decreased by 30% following the switch to degarelix. With the exception of injection site reactions, the overall prevalence and pattern of AEs during the first 3 months after the switch was comparable to that during the last 3 months leuprolide treatment in the main trial. There were five (4%) patients discontinued to treatment-related AEs including injection site pain (n = 3) and fatigue (n = 2). **Conclusions:** This 3-month analysis indicates that patients with prostate cancer can be safely switched from leuprolide to degarelix treatment with sustained efficacy as measured by biochemical markers.

What's known

- In a randomised 1-year trial, the GnRH antagonist, degarelix administered to prostate cancer patients resulted in a more rapid suppression of testosterone and PSA without testosterone surge during the first month compared with the GnRH agonist, leuprolide.
- Although these findings show major differences in the kinetics of testosterone and PSA suppression during the first month, there is currently no information available in the literature when switching from a GnRH agonist to a GnRH antagonist.

What's new

- Our trial demonstrates that prostate cancer patients can be successfully switched from leuprolide to degarelix treatment.
- In a planned analysis at 3 months, it was shown that patients can be safely switched from leuprolide to degarelix with sustained efficacy as measured by biochemical markers (testosterone and PSA).

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Disclosures
Jean de la Rosette has participated as an investigator in prostate cancer clinical studies for Ferring Pharmaceuticals and has received honoraria related to this work. He is also a paid consultant for BSC and Cook Medical. Ronald L Davis III received honoraria from Ferring Pharmaceuticals as an investigator in this study. David Frankel and Tine Kold Olesen are full time employees of Ferring Pharmaceuticals.

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Introduction

Androgen deprivation therapy (ADT) is commonly used in the management of advanced prostate cancer. Gonadotrophin-releasing hormone (GnRH) receptor agonists have been the treatment of choice for most patients for a number of years. GnRH receptor agonists effectively reduce serum testosterone levels to castrate levels (≤0.5 ng/ml) in 90–100% of patients, but only after 7–21 days (1,2). In addition, the agonists initially activate the GnRH receptors leading to a surge in serum LH and testosterone which might cause delayed therapeutic effects and exacerbation of symptoms such as spinal cord compression, bone pain and urethral obstruction (3–5). In contrast, the GnRH antagonist degarelix quickly binds to and blocks the GnRH receptors in the anterior pituitary gland which in turn results in rapid decreases in LH and FSH and ultimately in testosterone reaching castrate levels (≤0.5 ng/ml) within 1–3 days of subcutaneous (s.c.) administration (6–8).

More recently, GnRH antagonists also became available for physicians both in North America and Europe. In the pivotal, 1-year phase III trial, degarelix administered subcutaneous (s.c.) at a starting dose of 240 mg followed by monthly (every 28 days) maintenance doses of 80 mg (240/80 mg regimen) or 160 mg (240/160 mg regimen) was as effective as monthly intramuscular (i.m.) doses of 7.5 mg leuprolide in achieving and maintaining testosterone suppression at castrate level (≤0.5 ng/ml) with response rates ranging from 96.4% to 98.3% (7). In leuprolide-treated patients, testosterone surge occurred in 80% of the patients whilst none of the patients experienced this with degarelix. In line with the testosterone changes, PSA levels also declined

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more rapidly in the degarelix treatment groups during the first 28 days. While these findings highlight major differences in the kinetics of testosterone and PSA suppression with degarelix compared with leuprolide, there is currently no clinical information available in the literature describing switching patient medication from a GnRH agonist to a GnRH antagonist. The critical questions for the treating physician is whether the switch has any unexpected change in the pattern of efficacy of androgen deprivation therapy (ADT) and whether it is associated with any safety issues.

This clinical situation was addressed as part of an ongoing long-term extension trial to the aforementioned pivotal trial. In this extension trial, patients previously on degarelix continued with the same monthly degarelix maintenance doses, whereas those previously treated with leuprolide were re-randomised to receive degarelix at a starting dose of 240 mg followed by monthly maintenance doses of either 80 mg or 160 mg. Patients switched to degarelix were monitored closely during the initial 3-month period. A preplanned interim analysis of the data was scheduled when all patients had completed 3-months treatment at which time-point leuprolide plasma levels would also be negligible (9).

Patients and methods

Trial entry criteria in the main trial

The study design and the patient population participating in the study have been described previously in detail (7). In brief, patients were required to be ≥18 years with histologically confirmed adenocarcinoma of the prostate (all stages) for whom endocrine treatment (except for neoadjuvant hormonal therapy) was indicated. In addition, patients were required to have a screening testosterone level > 1.5 ng/ml and a PSA level ≥2 ng/ml. The trial was performed in accordance with the Declaration of Helsinki as well as Good Clinical Practice Guidelines.

In the original pivotal trial, prostate cancer patients received 1-year treatment with either monthly injections of leuprolide 7.5 mg i.m. or with degarelix at a starting dose of 240 mg s.c. followed by monthly maintenance doses of either 80 or 160 mg.

Design of extension trial

All patients who completed the initial comparative phase were eligible to enter the extension trial. Patients treated with degarelix continued with the same monthly maintenance doses while those patients who previously received treatment with leuprolide 7.5 mg were re-randomised to one of the two degarelix treatment regimens to receive a starting dose of 240 mg for 1 month followed by monthly maintenance doses of either 80 mg or 160 mg, respectively. Following the switch, patients were monitored closely and an interim analysis was performed according to trial protocol after all patients in the extension trial had been exposed to degarelix for at least 3 months. The results reported in this manuscript focus on the group of patients switched from leuprolide to degarelix and treated with these treatment regimens for 3 months.

Trial parameters and data analysis

Efficacy assessments included changes in serum hormone (testosterone, LH and FSH) and PSA levels which were measured by a central laboratory (Esoterix Inc., Calabasas, CA, USA). Serum testosterone levels were determined using a validated liquid chromatography with tandem mass spectrometry assay with a lower limit of quantitation of 0.03 ng/ml. Testosterone was measured in triplicates and the median value is reported. PSA analyses were performed using a validated immunoassay. LH and FSH analyses used validated immunochemiluminometric methods. Safety and tolerability assessments included laboratory values (biochemistry, haematology and urinalysis), clinical parameters [adverse events (AEs), ECGs, physical examination and vital signs]. Global Central Labs PPD performed the analyses of all clinical chemistry, haematology and urinalysis parameters.

Baseline characteristics were summarised by descriptive statistics. Serum levels of testosterone, PSA, LH and FSH at baseline of the main and the extension trials are shown with median values and interquartile ranges. Changes of the biomarkers are illustrated by median levels over time (testosterone) and median percentage changes from baseline (LH, FSH and PSA). Prevalence rates of AEs (at least 3%) were summarised during the first and the last 3 months of the main trial and the first 3 months of the extension trial for comparative purposes.

Results

The extension trial was initiated in March 2007 and by February 2008 all patients had been treated with degarelix for at least 3 months. Of the 172 completers of the main trial in the leuprolide arm, 135 patients were re-randomised and 134 patients were treated with degarelix in the extension trial. During the first 3 months of treatment with degarelix, 13 (10%) patients discontinued the trial [8 (12%) degarelix 240/80 mg and 5 (8%) degarelix 240/160 mg]. The patient flow and reasons for discontinuation are displayed by treatment group in Figure 1.

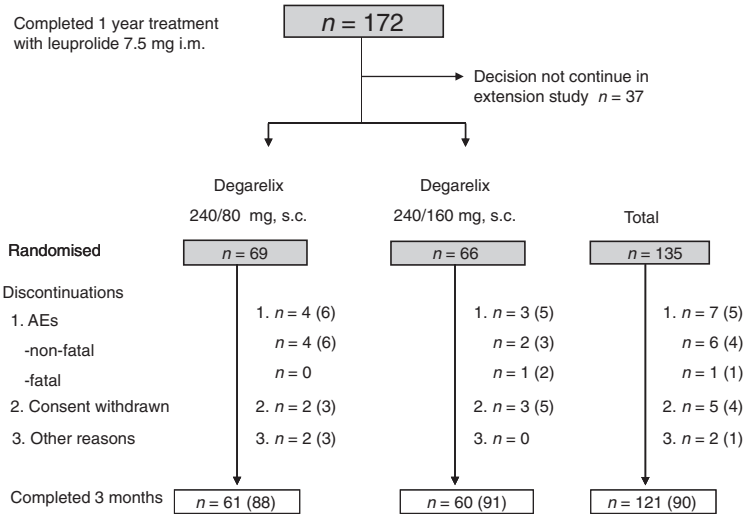

Figure 1 Patient flow during the first 3 months of treatment with degarelix in the extension trial for patients who switched from leuprolide. Numbers in parenthesis denote the percentage of randomised patients of that treatment group

Demographics and baseline characteristics

The baseline and disease characteristics are shown in Table 1. Baseline median testosterone, PSA, LH and FSH levels are presented for both prior to the main trial and at the time of the switch (after 1-year treatment with leuprolide). Baseline and disease characteristics for patients switching from leuprolide to degarelix treatment were comparable and representative of the initial population treated with leuprolide.

Testosterone levels

The median testosterone levels over time from the start (baseline) of the main trial and for those patients continuing in the extension trial, up to 84 days after the start of the extension trial are displayed in Figure 2A. In the extension phase, serum testosterone levels were ≤0.5 ng/ml from day 3 to day 84. Testosterone levels remained suppressed and during the first 84 days after the switch from leuprolide to degarelix treatment the median testosterone levels were 0.1 ng/ml. One patient with a serum testosterone level 1.4 ng/ml at the time of the switch, had serum testosterone levels ≤0.5 ng/ml from day 3–84 during degarelix treatment. At the time of database cut-off, one patient in the leuprolide 7.5 mg/degarelix 240/80 mg group had testosterone levels > 0.5 ng/ml on consecutive occasions after day 84.

LH and FSH levels

The median percent reduction in LH over time from the start of the main trial (baseline) to day 84 in the extension trial is displayed in Figure 2B. There was a similar pattern of changes in LH levels as with testosterone. The approximate 99% reduction in median LH levels was maintained after the switch from leuprolide to degarelix treatment.

The median percent reduction in FSH over time from the start of the main trial (baseline) to day 84 in the extension trial is displayed in Figure 2C. FSH levels decreased rapidly with approximate maximum reductions of 90% at 28 days after the initial degarelix doses and after 1-year treatment FSH levels were reduced to about 82% relative to baseline. For leuprolide, there was an initial increase of FSH level followed by a decrease of about 75% at day 28. After 1-year treatment with leuprolide FSH levels were reduced to about 55% relative to baseline. Interestingly, after the treatment switch, FSH levels were further reduced to about 80% relative to baseline.

PSA levels

The median percent reduction in PSA over time from the start (baseline) is displayed in Figure 2D. PSA levels were reduced more rapidly during the first 28 days of treatment in the degarelix treatment groups with median reductions of about 65% and 83% at day 14 and day 28, respectively, compared with corresponding median decreases in PSA of approximately 20% and 68% in the leuprolide treatment arm. Thereafter, PSA levels were reduced to a similar extent in the degarelix and leuprolide treatment groups and after 1 year treatment there was ≥95% reduction in PSA from baseline in all treatment groups. The ≥95% median reduction of PSA levels was maintained after switching from leuprolide to degarelix treatment, and during the first 84 days of treatment with degarelix. The median PSA levels were 0.5 ng/ml or less.

Table 1 Patient demographics and baseline characteristics

	Leuprolide 7.5 mg/Degarelix 240/160 mg	Leuprolide 7.5 mg/Degarelix 240/80 mg	Leuprolide 7.5 mg (main trial)
Safety analysis set	65	69	201
Median age (years)	73.0 (52–92)	74.0 (52–98)	74.0 (52–98)
Median (25–75 percentile)			
Testosterone, ng/ml (main)	3.5 (3.0–4.9)	4.3 (3.4–5.3)	3.8 (2.9–5.0)
Testosterone, ng/ml (ext)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	
PSA, ng/ml (main)	14.0 (7.9–32.4)	25.7 (9.8–131.1)	17.4 (8.4–56.5)
PSA, ng/ml (ext)	0.4 (0.1–1.1)	0.4 (0.1–6.2)	
LH, IU/l (main)	5.5 (3.7–7.3)	6.6 (4.1–10.0)	6.0 (4.1–9.5)
LH, IU/l (ext)	0.0 (0.0–0.0)	0.0 (0.0–0.1)	
FSH, IU/l (main)	8.2 (4.6–12.7)	8.7 (5.9–14.9)	8.7 (5.9–14.1)
FSH, IU/l (ext)	4.4 (3.4–5.7)	4.8 (3.4–6.5)	
Stage of PCa			
Localised*	19 (29%)	20 (29%)	63 (31%)
Locally advanced†	24 (37%)	18 (26%)	52 (26%)
Metastatic	9 (14%)	21 (30%)	47 (23%)
Not classifiable	13 (20%)	10 (14%)	39 (19%)
Curative intent‡			
Yes	5 (8%)	6 (9%)	24 (12%)
No	60 (92%)	63 (91%)	177 (88%)
Gleason score§			
2–4	11 (17%)	8 (12%)	24 (12%)
5–6	18 (28%)	25 (36%)	63 (32%)
7	18 (28%)	17 (25%)	62 (31%)
8–10	17 (26%)	19 (28%)	51 (26%)

*Localised = T1/2, NX or N0. †Locally advanced = T 3/4, NX or N0, and M0, or N1 and M0. ‡Curative intent defined as previous radical prostatectomy or radiotherapy. §Gleason score is sum of the Gleason grade of the primary and secondary patterns.

Safety and tolerability

The prevalence of treatment-emergent AEs (at least 3%) for the first and last 3 months treatment with leuprolide 7.5 mg in the main trial and during the first 3 months after the switch from leuprolide to degarelix is displayed in Table 2. Adverse events are grouped according to domains of local tolerability, ADT-related, disease-related and 'other' AEs. Except for local tolerability injection site reactions, the overall prevalence and pattern of AEs during the last 3 months of leuprolide treatment in the main trial was comparable to those after the switch from leuprolide to degarelix.

Injection site reactions were the most frequently reported AEs associated with the switch. The local reactions occurred primarily after the first injection with 28% of 134 starting dose injections reported to be associated with injection site reactions. However, only 6% of 125 (leuprolide/degarelix 240/160 mg) and 3% of 127 (leuprolide/degarelix 240/80 mg) maintenance dose injections during the first 3 months were reported to be associated with injection site reactions. The most common types of injection site reactions were pain and erythema.

After the switch from leuprolide to degarelix, 5 (7% and 8%) patients in both dose groups had serious adverse events (SAEs) in the first 3 months. These SAEs also included two (3%) patients with prostate cancer (PCa) progression in the leuprolide 7.5 mg/degarelix 240/160 mg group. Importantly, none of the SAEs was considered as related to degarelix treatment. Two patients died as a result of PCa progression and PSA levels were already increasing during the last 3–6 months on leuprolide.

There were seven (5%) patients who discontinued from the extension trial within 3 months (up to 91 days) after switching from leuprolide to degarelix because of AEs. These included three patients with injection site pain and two patients with fatigue (started during treatment with leuprolide in main trial); the injection site pain and fatigue were assessed as possibly or probably related to degarelix.

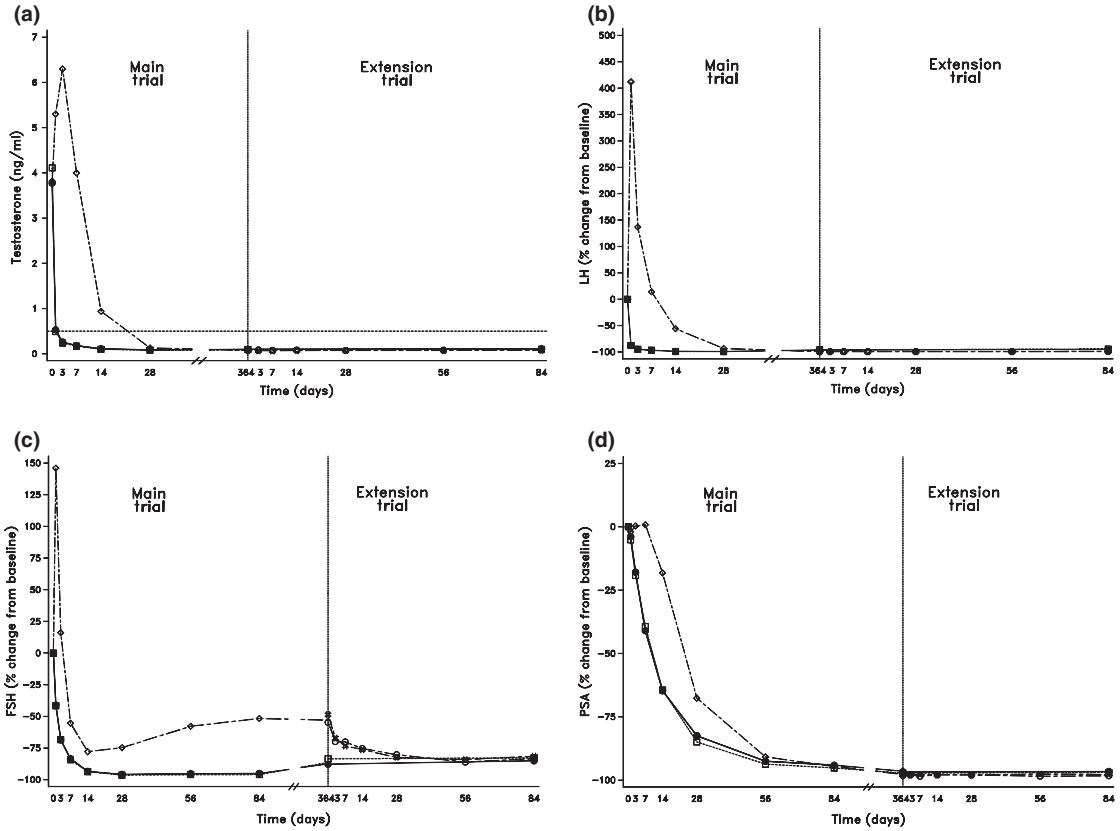

Figure 2 Median serum (A) testosterone (ng/ml) and median percent change from baseline for (B) LH levels (C) FSH levels and (D) PSA levels. ●———●: degarelix 240/160 mg; □– – – –□: degarelix 240/80 mg; ◇– —— –◇: leuprolide 7.5 mg; #– —— –# leuprolide 7.5 mg/degarelix 240/160 mg; ○– —— –○: leuprolide 7.5 mg/degarelix 240/80 mg

The remaining two patients were discontinued from the trial as a result of prostate cancer progression (not treatment-related).

Overall five (4%) patients had prostate cancer progression reported as a new AE during the first 3 months after the switch from leuprolide to degarelix treatment. Four of the patients with prostate cancer progression had metastatic prostate cancer and one patient had locally advanced prostate cancer and PSA levels prior to starting leuprolide treatment ranged from 619 ng/ml to 10,952 ng/ml. In addition, PSA levels were increasing in these five patients during the last 3–6 months of leuprolide therapy. Following the switch, PSA levels continued to increase during degarelix treatment in these patients.

There were a few patients with laboratory abnormalities including one additional (2%) patient in the leuprolide 7.5 mg/degarelix 240/80 mg treatment groups who had alanine aminotransferase (ALT) levels of more than three times the upper limit of normal range (ULN) during the first 3 months of the extension trial. The increase in ALT was reversible. In addition to the laboratory liver function test abnormalities, there was one patient in the leuprolide 7.5 mg/degarelix 240/80 mg group with a serum urea nitrogen > 10.7 mmol/l, two patients in both the leuprolide 7.5 mg/degarelix 240/160 mg and 240/80 mg treatment groups with a low haematocrit ratio of ≤0.37 and one patient in the leuprolide 7.5 mg/degarelix 240/160 mg with a low haemoglobin level (≤115 g/l).

Discussion

Androgen deprivation therapy, ADT, is commonly used in the management of prostate cancer and there may be situations where the treating physician and/or patient want to try an alternative form of androgen deprivation therapy. For example, if a patient is chronically bothered by adverse effects commonly associated with a GnRH agonist, it could be an option to consider switching to a GnRH antagonist instead. In the pivotal Phase 3 trial (7), there was a significantly lower incidence of musculoskeletal (arthralgia) adverse events (4% vs. 9%) and urinary tract infection (3% vs. 9%) with degarelix as compared with leuprolide. Furthermore, the GnRH blocker could be considered if a patient does not

Table 2 Prevalence of treatment-emergent AEs during the first and last 3 months in the main trial and the first 3 months after the switch from degarelix to leuprolide in extension trial (at least 3% in any group)

AE, *n* (%)	Leuprolide 7.5 mg Q1, main trial	Leuprolide 7.5 mg Q4, main trial	Leuprolide 7.5 mg Degarelix 240/160 mg and 240/80 mg Q1, ext. trial
Safety analysis set	201	180	134
Any AE	78 (39)	102 (57)	86 (64)
Local tolerability	0	0	40 (30)
Injection site pain	0	0	31 (23)
Injection site erythema	0	0	20 (15)
Injection site swelling	0	0	7 (5)
Injection site inflammation	0	0	5 (4)
ADT-related	49 (24)	71 (39)	52 (39)
Hot flush	35 (17)	29 (16)	19 (14)
Weight increase	0	24 (13)	21 (16)
Fatigue	5 (2)	10 (6)	10 (7)
Erectile dysfunction	5 (2)	9 (5)	6 (4)
Hypertension	2 (1)	7 (4)	5 (4)
Anaemia	2 (< 1)	6 (3)	6 (4)
Depression	0	7 (4)	6 (4)
Insomnia	2 (< 1)	3 (2)	5 (4)
Disease-related	26 (13)	41 (23)	32 (24)
Arthralgia	8 (4)	12 (7)	7 (5)
Back pain	6 (3)	11 (6)	6 (4)
UTI	9 (4)	6 (3)	5 (4)
Weight decrease	1 (< 1)	8 (4)	8 (6)
Constipation	4 (2)	7 (4)	5 (4)
Pain in extremity	3 (1)	4 (2)	5 (4)
Prostate cancer progression	0	3 (2)	7 (5)
Other	9 (4)	15 (8)	15 (11)
Dizziness	7 (3)	3 (2)	4 (3)
ALT increase	2 (< 1)	6 (3)	6 (4)
AST increase	1 (< 1)	4 (2)	5 (4)
Gamma-glutamyl transferase increase	0	3 (2)	5 (4)
Peripheral oedema	0	6 (3)	3 (2)

Values given in bracket are expressed in percentage.

achieve and/or sustain testosterone suppression at castrate levels on the agonist [failure rate is ~10% (10–12)]. Insufficient testosterone suppression may have safety implications for the management of persisting pain, urinary symptoms or even for disease progression (13,14), but this may also be an issue when the therapy targets rapid shrinkage of the prostate before high-dose radiotherapy (13). The most recent safety concern related to GnRH agonists is the cardiovascular risk (myocardial infarction, stroke, sudden death), which had to be added to the Warnings and Precautions section of the drug labels upon request by FDA in October 2010 (15). This warning does not yet apply to the GnRH antagonists and switching patients with established cardiovascular disease – who are at the greatest risk of complications (16) – could be considered. Regarding the financial implications of the switch, the average sales price (ASP) to Medicare in the US for a year supply of degarelix [(FIRMAGON) starting dose 240 mg, maintenance dose 80 mg/month] is 2659 US dollars which is comparable to the ASP for leuprolide [(LUPRON) 7.5 mg/month] of 2357 US dollars.

There is currently no information available in the literature when switching from a GnRH agonist to a GnRH antagonist and this was investigated as part of an ongoing long-term extension trial. An interim analysis of the data was scheduled when all patients had completed 3 months treatment and the main purpose of this analysis was to confirm that there

was no unexpected safety or lack of efficacy issues associated with switching patients from leuprolide to degarelix treatment.

The dosing regimens were selected for optimal treatment for patients who switched from leuprolide to degarelix and included a starting dose of 240 mg degarelix followed by monthly maintenance doses of either 80 or 160 mg. It has been established in previous dose-finding trials (6,17) that an initial starting dose of 240 mg degarelix is required in order to achieve sufficient suppression of testosterone to castrate levels (≤0.5 ng/ml) in 95% of patients for at least 28 days. In addition, subsequent to the starting dose, lower monthly maintenance doses are effective in producing sustained testosterone suppression (6–8). The principle of using a high-loading dose followed by low maintenance doses to effectively suppress testosterone, LH and FSH has also been demonstrated in healthy men who were treated with the GnRH antagonist, cetrorelix (18).

When switching from leuprolide to degarelix, testosterone suppression was maintained at castrate levels from day 3–84 in all patients and the median testosterone level was 0.1 ng/ml. One of the leuprolide-treated patients had a serum testosterone level of 1.4 ng/ml, which was rapidly suppressed to < 0.5 ng/ml by degarelix, suggesting that a switch can potentially be beneficial in those with insufficient testosterone suppression on the agonist.

Follicle-stimulating hormone (FSH) levels that had decreased by 50% from baseline after 1 year of treatment with leuprolide were further decreased to 80% reduction from baseline following the switch to degarelix. It has been shown in previous studies that FSH levels are decreased more rapidly and to a greater extent with degarelix (7) and another GnRH antagonist, abarelix (19,20) than with leuprolide. In addition to its role in the maintenance of spermatogenesis (21) in adult men, there is some evidence that FSH may be a regulator of bone resorption (22) and hence increases in FSH could drive bone loss. In a recent clinical trial in postmenopausal women (23), it was demonstrated that FSH receptor polymorphisms influence bone mineral density (BMD) and bone turnover. Thus, the stronger suppression of FSH by the antagonist suggests a potential safety benefit, which requires further exploration in a larger comparative study addressing BMD changes and fracture risk.

Suppression of PSA levels was maintained after the treatment switch. During the first 84 days of degarelix treatment, the median PSA levels were ≤0.5 ng/ml. There were five (4%) patients with prostate cancer progression reported as a new AE. This was not unexpected since PSA levels were already rising during the last 3–6 months of leuprolide treatment. Four of the patients with prostate cancer progression had metastatic prostate cancer and one patient had locally advanced disease with high baseline PSA levels ranging from 619 to 10,952 ng/ml. Thus, these results suggest that while degarelix keeps PSA suppression sustained in patients with hormone-sensitive tumours, it may not be able to provide added benefits in those with very progressive cancer disease or already castration-resistant tumours (24).

After switching from leuprolide to degarelix treatment, degarelix was well tolerated. The pattern of AEs included those related to ADT therapy and AEs occurring as a consequence of the primary disease as expected in this patient population. The prevalence rates of these events during the first 3 months after the switch to degarelix were comparable with those during the last 3 months on leuprolide. The most frequently reported local tolerability reactions which occurred after the switch to degarelix were injection site pain and erythema. The injection site reactions occurred typically after the loading injection with a much lower incidence after subsequent dosing. This observation is consistent with results in the main 1-year trial (7) and is probably attributable to the higher dose/volume given for the first time (two injections as opposed to one injection for subsequent doses). During the first 3 months of degarelix treatment, only 2% of patients discontinued as a result of injection site pain, indicating that overall benefits outweigh the relative inconvenience of an injection site reaction. The two other treatment-related discontinuations were attributable to fatigue which had, however, already started during the initial treatment with leuprolide. With the exception of injection site reactions, the overall pattern and prevalence of adverse events during the first 3 months after the switch from leuprolide to degarelix were comparable to that reported during the last 3 months of leuprolide treatment in the main trial.

Conclusions

This 3-month analysis indicates that patients with prostate cancer can be safely switched from leuprolide to degarelix treatment. After switching to a starting dose of 240 mg degarelix followed by monthly administration of degarelix, at doses of 80 mg or 160 mg, effective suppression of LH and testosterone (at castrate levels) and PSA are all maintained accompanied by further decreases in FSH levels. Data from currently ongoing long-term studies are awaited to further explore the clinical significance of these changes in biochemical markers.

Author contributions

Tine Kold Olesen was involved in the study design, and all authors contributed to the conduct or data analysis/interpretation of the study. David Frankel was responsible for the original draft of the article. All authors were involved in the critical revision of the manuscript and approved the submitted version of the article.

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