Intermittent Androgen Deprivation with the GnRH Antagonist Degarelix in Men with Biochemical Relapse of Prostate Cancer

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Abstract

Objective: To determine if 7 months of intermittent degarelix treatment is noninferior to continuous androgen deprivation in maintaining suppression of prostate-specific antigen (PSA) at 14 months.

Patients and Methods: Patients with rising PSA after prior definitive therapy were randomized to intermittent (degarelix) or continuous (degarelix or leuprolide) treatment arms. All patients initially received 7 months of androgen deprivation. After 7 months, men randomized to intermittent therapy were scheduled to enter a 7-month off-treatment period; degarelix was restarted if PSA levels were >2 ng/mL. Predefined criteria for noninferiority of the primary endpoint, proportion of patients with PSA ≤4 ng/mL, was the lower limit of the 95% CI difference between the intermittent and continuous treatment arms being greater than -12.5% at month 14. PSA, testosterone, and quality-of-life measures were assessed in all patients at multiple time points.

Results: A total of 409 patients were randomized to intermittent (degarelix, n = 177) or continuous (degarelix, n = 50; leuprolide, n = 182) treatment. At month 14, the lower confidence interval limit for intermittent versus continuous treatment was -0.19%; therefore, noninferiority was established. No patients in the intermittent arm had PSA >4 ng/mL at month 14, although 35 patients restarted degarelix before month 14. PSA was >4 ng/mL in 3 (1.6%) patients receiving continuous treatment. In the intermittent arm, 116 (85%) men had testosterone >0.5 ng/mL at a median of 112 days off therapy (95% CI, 112-140). Intermittent treatment was associated with improved sexual drive assessed by the sexual function inventory at month 14 ($P = 0.027$). The most frequently reported adverse event in all arms was hot flashes. Injection site reactions were more frequent in patients receiving degarelix.

Conclusion: Intermittent degarelix administered as described is noninferior to continuous androgen deprivation in maintaining PSA suppression at month 14. These data indicate that degarelix is a suitable treatment option in men being considered for intermittent androgen ablation.

Key words: Degarelix, intermittent androgen deprivation, leuprolide, quality of life, testosterone

Introduction

Androgen deprivation therapy (ADT) is the mainstay of treatment for men with metastatic prostate cancer (PCa) and has been shown to improve survival in combination with radiation therapy in men with high-risk localized disease.[1-3] It is also commonly used to treat men with biochemical relapse, especially when classified as high risk. Unlike bilateral orchiectomy, medical castration is reversible and may be used on an intermittent basis. ADT is associated with characteristic side effects including hot flashes; decreased libido, bone mineral density, body mass, muscle mass, and strength; increased body fat, weight; insulin resistance; cardiovascular toxicity; and emotional and cognitive changes.[4,5] The potential physical benefits of an intermittent regimen with one or more off-treatment periods are considered to be due to complete or partial testosterone recovery allowing moderation of side effects and improvement of quality of life (QoL).[6]

Two phase III noninferiority trials of luteinizing hormone-releasing hormone (LHRH) agonists have compared intermittent androgen deprivation (IAD) with continuous androgen deprivation (CAD).[7,8] The National Cancer Institute of Canada trial, PR-7 (NCT00003653), enrolled patients with biochemical failure after primary or salvage radiotherapy for localized disease.[7] IAD was noninferior to CAD for overall survival (8.8 vs 9.1 years, respectively; HR = 1.02), and scores for hot flashes, desire for sexual activity, and urinary symptoms were significantly improved. Also, men in the CAD arm of PR-7 who achieved nadir testosterone levels <20 ng/mL had an increased time to hormone resistance, demonstrating the importance of achieving low testosterone levels while on treatment.[9]

The second trial, SWOG 9346 (NCT00002651), compared IAD with CAD for patients diagnosed with metastatic disease (median follow-up, 9.8 years).[8] Median survival was 5.8 years and 5.1

TABLE 1. Patient Demographics and Baseline Characteristics (at enrollment)

Variable	Intermittent degarelix	Continuous degarelix	Continuous leuprolide	Combined continuous arms	Total
FAS, n	175	50	178	228	403
Median age, years (range)	73 (50–91)	71 (56–88)	71 (51–89)	71 (51–89)	72 (50–91)
Median baseline BMI, kg/m^2 (range)	27.8 (16.3–51.2)	28.1 (20.4–40.7)	28.8 (17.8–49.5)	28.7 (17.8–49.5)	28.3 (16.3–51.2)
Median testosterone, ng/mL (range)	3.51 (0.8–9.62)	3.56 (1.2–9.21)	3.51 (0.62–7.84)	3.54 (0.62–9.21)	3.51 (0.62–9.62)
Median PSA, ng/mL (range)	5.15 (0.2–655)	6.45 (0.31–214)	4.52 (0.17–262)	4.96 (0.17–262)	5.1 (0.17–655)
Disease stage, n (%)					
Localized	65 (37)	17 (34)	60 (34)	77 (34)	142 (35)
Locally advanced	7 (4)	1 (2)	13 (7)	14 (6)	21 (5)
Metastatic	0 (0)	0 (0)	1 (<1)[b]	1 (<1)	1 (<1)
Not classifiable[a]	103 (59)	32 (64)	104 (58)	136 (60)	239 (59)
Gleason score (at diagnosis)					
2–4	4 (2)	1 (2)	3 (2)	4 (2)	8 (2)
5–6	56 (32)	22 (44)	61 (35)	83 (37)	139 (35)
7–10	115 (66)	27 (54)	112 (64)	139 (62)	254 (63)
Primary therapy[c]					
Radical prostatectomy	39 (22)	10 (20)	38 (21)	48 (21)	87 (22)
Radiotherapy	107 (61)	33 (66)	120 (67)	153 (67)	260 (65)
Cryotherapy	24 (14)	6 (12)	17 (10)	23 (10)	47 (12)
Other	5 (3)	1 (2)	2 (1)	3 (1)	8 (2)
Not recorded	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)

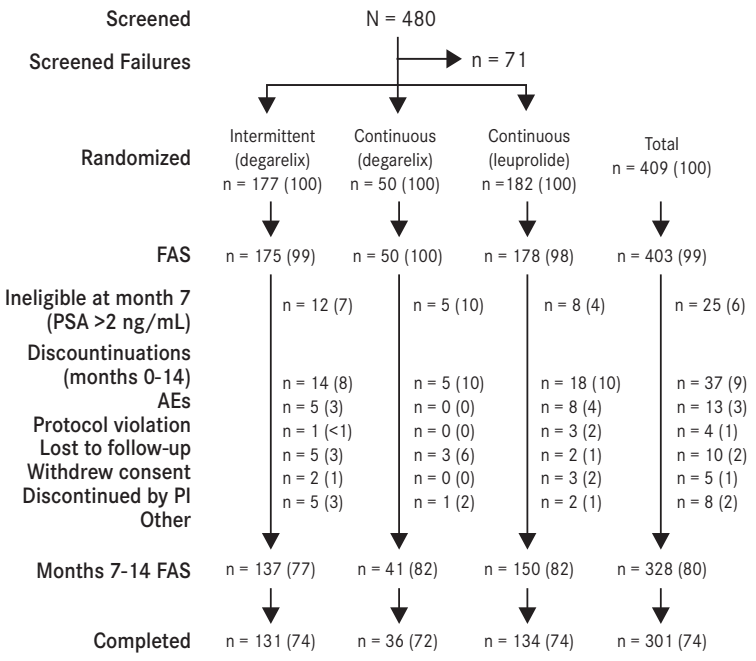
[a]As only a scan was required for study entry, "not classifiable" was chosen when an investigator could not medically conclude that a subject's prostate cancer was definitely localized, locally advanced, metastatic.
[b]Patient data were censored at 1 month and 4 days after initiation of drug treatment, contrary to trial protocol.
[c]Primary (definitive) data were recorded at screening.

years in the CAD and IAD arms, respectively (HR = 1.10). Although survival noninferiority for IAD was inconclusive, IAD was associated with better erectile function and mental health 3 months after discontinuing ADT in the IAD arm compared withthe CAD arm.

Degarelix is a gonadotropin-releasing hormone (GnRH) antagonist providing rapid and sustained testosterone suppression, yet, it has a short half-life of approximately 4 weeks.[10,11] Unlike LHRH agonists, GnRH antagonists immediately suppress the secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone without initially overstimulating the GnRH receptor. Thus, there is no transient increase in testosterone, no need for flare protection with an antiandrogen, and a more rapid castration,[10] which may be favorable characteristics for IAD therapy.

A recent noncomparative study of European men with histologically confirmed prostate cancer requiring ADT demonstrated that IAD with degarelix was well tolerated, and increases in testosterone were associated with improved erectile function prior to prostate-specific antigen (PSA) reaching the predefined level at which treatment was reinitiated (>4 ng/mL).[12] The current trial aimed to determine if intermittent use of a GnRH antagonist, degarelix, is non-inferior to continuous use of an LHRH agonist in maintaining a pre-specified level of PSA suppression at month 14 (≤4 ng/mL) while evaluating testosterone levels and potential impact on QoL. Non-inferiority in regards of PSA levels was established if the lower limit of the 95% CI difference between the intermittent and continuous treatment arms was greater than -12.5%, a predefined difference considered not clinically relevant. Addressing this endpoint will provide preliminary data as to whether an antagonist such as degarelix is equivalent to LHRH agonists when used as intermittent therapy and assess tolerability compared with continuous ADT.

FIGURE 1. Patient Flow



Patient flow (numbers in parenthesis denote percentage of randomized patients for that treatment arm). FAS, full analysis set.

Patients and Methods

Study Design: This open-label, controlled, parallel-arm, multicenter trial (NCT00928434) randomized patients 7:2:7 to intermittent (degarelix; n = 177) or continuous (degarelix; n = 50; leuprolide; n = 182) treatment, respectively. Randomization lists were prepared centrally (Department of Global Biometrics, Ferring Pharmaceuticals A/S) using a validated computer program. The trial was conducted in accordance with the Declaration of Helsinki, with applicable FDA regulations and the International Conference on Harmonization Guidelines for Good Clinical Practice. Appropriate Institutional Review Boards for each site approved the study protocol and amendments, and all patients provided written, informed consent.

Patient Selection: Men ≥18 years with histologically confirmed prostate adenocarcinoma and a negative bone scan with rising serum PSA levels after prior definitive therapy for whom hormone therapy was indicated were eligible. The minimum criteria were screening serum testosterone ≥1.5 ng/mL, Eastern Cooperative Oncology Group score ≤2, and a rise in PSA of ≥0.2 ng/mL following radical prostatectomy or 3 separate PSA levels higher than nadir PSA after other primary therapy. Exclusion criteria included hormone therapy within 6 months or bicalutamide within 2 months of randomization. Patients receiving neoadjuvant hormone therapy for more than 4 months or adjuvant hormone therapy for more than 6 months were excluded.

Treatment Plan and Toxicity Evaluation: The initiation phase comprised 7 months of degarelix 1-month depot formulation (starting dose 240 mg; 6 monthly 80-mg maintenance doses) or leuprolide (1-month injection [7.5 mg] and two 3-month [22.5 mg] injections). Patients with PSA ≤2 ng/mL at month 7 entered a second 7-month phase. Intermittent arm patients entered an off-treatment period. If PSA increased to >2 ng/mL, degarelix was reintroduced (240 mg followed by 80 mg monthly) until PSA was ≤2 ng/mL or the investigator determined the patient needed another treatment. Patients in the continuous treatment arms were maintained on monthly degarelix or leuprolide every three months. Blood samples for testosterone and PSA were obtained monthly and analyzed at a certified central laboratory. Serum testosterone levels were determined using a validated liquid chromatography system with tandem mass spectrometry assay. PSA was analyzed using a validated immunoassay.

The safety analysis set comprised all men who received at least one dose of ADT and included laboratory values (biochemistry, hematology, and urine analysis) and clinical variables (including patient-reported injection-site tolerability, adverse events (AEs), electrocardiograms, and physical examination). AEs were graded according to National Cancer Institute Common Terminology Criteria for AEs (Version 4.02).

Response Evaluation: The primary endpoint was the proportion of patients with serum PSA ≤4.0 ng/mL at month 14 for intermittent degarelix treatment vs continuous therapy (degarelix and leuprolide arms combined). Noninferiority was established if the lower limit of the 95% CI difference between the intermittent and continuous treatments was greater than -12.5%. Secondary endpoints included time to PSA >2 ng/mL in the intermittent arm during off-treatment time vs continuous therapy, time to testosterone >0.5 ng/mL and ≥1.5 ng/mL in the intermittent arm, proportion of intermittent-arm patients requiring additional degarelix dosing, development of castration resistance (2 consecutive rises in PSA ≥2 weeks apart and 50% greater than nadir despite castrate levels of testosterone),[13,14] and disease progression (rising PSA despite castrate testosterone levels, additional PCa therapy, or death from any cause). Efficacy endpoints were assessed at month 14 in all patients eligible for the second phase (with at least one primary endpoint efficacy measurement between months 7 – 14).

Additional secondary endpoints relating to QoL and sexu-

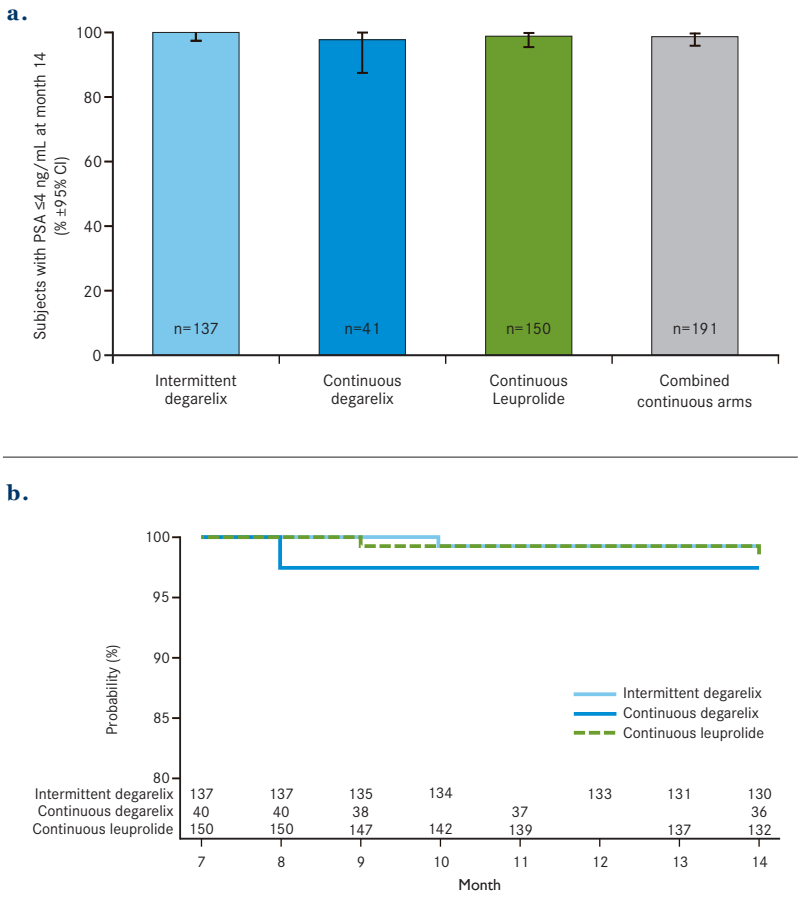
TABLE 2. Treatment-Emergent AEs With an Overall Incidence of ≥5% by MedDRA Preferred Term (Safety Analysis Set)

Summary of AEs	Intermittent degarelix n = 175, n (%)			Continuous degarelix n = 50, n (%)			Continuous leuprolide n = 178, n (%)		
All AEs	159 (91)			47 (94)			158 (89)		
AEs leading to discontinuation	14 (8)			5 (10)			18 (10)		
Deaths*	2 (1)			0 (0)			2 (1)		
AEs by grade**	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Hot Flashes	61 (35)	23 (13)	5 (3)	16 (32)	9 (18)	1 (2)	81 (46)	24 (13)	6 (3)
Injection site reactions									
Injection site pain	72 (41)	25 (14)	0 (0)	28 (56)	10 (20)	1 (2)	17 (10)	5 (3)	0 (0)
Injection site erythema	37 (21)	12 (7)	0 (0)	16 (32)	4 (8)	1 (2)	1 (<1)	0 (0)	0 (0)
Injection site swelling	19 (11)	4 (2)	0 (0)	5 (10)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site edema	5 (3)	3 (2)	0 (0)	3 (6)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site induration	1 (<1)	0 (0)	0 (0)	3 (6)	2 (4)	1 (2)	0 (0)	0 (0)	0 (0)
Fatigue	24 (14)	5 (3)	3 (2)	9 (18)	0 (0)	1 (2)	21 (12)	11 (6)	0 (0)
Cough	4 (2)	3 (2)	0 (0)	5 (10)	2 (4)	0 (0)	2 (1)	1 (<1)	0 (0)
Arthralgia	5 (3)	8 (5)	0 (0)	3 (6)	2 (4)	0 (0)	12 (7)	7 (4)	0 (0)
Hypertension	6 (3)	6 (3)	0 (0)	2 (4)	2 (4)	0 (0)	5 (3)	13 (7)	0 (0)
Constipation	8 (5)	1 (<1)	0 (0)	3 (6)	1 (2)	0 (0)	4 (2)	7 (4)	1 (<1)
Urinary tract infection	1 (<1)	5 (3)	0 (0)	2 (4)	3 (6)	0 (0)	4 (2)	10 (6)	0 (0)
Nausea	5 (3)	4 (2)	1 (<1)	2 (4)	2 (4)	0 (0)	3 (2)	2 (1)	0 (0)
Hematuria	5 (3)	3 (2)	0 (0)	3 (6)	1 (2)	0 (0)	6 (3)	3 (2)	0 (0)
Back pain	3 (2)	5 (3)	0 (0)	2 (4)	1 (2)	0 (0)	5 (3)	5 (3)	0 (0)
Nasopharyngitis	2 (1)	5 (3)	0 (0)	2 (4)	1 (2)	0 (0)	4 (2)	7 (4)	0 (0)
Procedural pain	1 (<1)	5 (3)	1 (<1)	0 (0)	3 (6)	0 (0)	2 (1)	7 (4)	1 (<1)
Diarrhea	8 (5)	2 (1)	0 (0)	3 (6)	0 (0)	0 (0)	4 (2)	2 (1)	0 (0)
Sinusitis	3 (2)	6 (3)	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	3 (2)	0 (0)
Headache	7 (4)	3 (2)	0 (0)	1 (2)	0 (0)	0 (0)	5 (3)	4 (2)	0 (0)
Dizziness	6 (3)	5 (3)	0 (0)	2 (4)	0 (0)	0 (0)	5 (3)	1 (<1)	0 (0)
Upper respiratory tract infection	3 (2)	4 (2)	0 (0)	1 (2)	0 (0)	0 (0)	4 (2)	7 (4)	0 (0)
Pyrexia	2 (1)	3 (2)	0 (0)	3 (6)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)
Bronchitis	1 (<1)	5 (3)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	1 (<1)	0 (0)
Dysuria	0 (0)	4 (2)	0 (0)	3 (6)	0 (0)	0 (0)	3 (2)	0 (0)	0 (0)
Dyspepsia	0 (0)	1 <1()	0 (0)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Nasal congestion	1 (<1)	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	2 (1)	0 (0)	0 (0)
Epistaxis	0 (0)	0 (0)	0 (0)	2 (4)	1 (2)	0 (0)	0 (0)	1 (<1)	0 (0)

*No deaths were considered related to study treatment (causes of death in the intermittent arm were cardio-respiratory arrest, sepsis, and/or bile duct cancer; in the continuous leuprolide arm, myocardial infarction and renal failure).
**Mild, moderate and severe relate to CTCAE grades 1, 2 and 3, respectively.

al function were assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) and the sexual function inventory (SFI), respectively. FACT-P was completed at every visit during the study and assesses physical, social/family, emotional, and functional well-being, as well as prostate-related symptoms. The SFI was completed at baseline, visit 4, and prior to stopping treatment. During the off-treatment phase, the SFI was completed every 2 months and at the end-of-trial visit. It is a widely used, multidimensional, self-report instrument specifically designed to evaluate sexual function and satisfaction of men on treatment or

FIGURE 2.



Proportion of patients with (a) serum PSA ≤4.0 ng/mL (± 95% CI) at month 14 (last observation carried forward) and (b) time to PSA >4.0 ng/mL during months 7-14.

with conditions that may affect sexual function.

Statistical Analysis: Primary endpoint response rates between intermittent and continuous therapy were compared using Fisher's exact test and the confidence interval determined using a normal approximation to the binomial distribution. Assuming a common response rate of 80% of patients with PSA <4 ng/mL at month 14 and adjusting for patients potentially discontinued after 7 months, 175 patients in both the intermittent degarelix and continuous leuprolide arms and 50 in the continuous degarelix arm would give 80% power to detect a non-inferiority limit of -12.5%. Secondary endpoints comprising time-to-event variables were assessed by the Kaplan-Meier method and log-rank test. QoL and SFI outcomes were assessed by cross-sectional analyses of covariance (ANCOVA) using baseline values as a covariate. Exploratory sub-analyses for the intermittent arm included time to testosterone >0.5 ng/mL according to age, baseline PSA, disease stage, and PSA at month 7. Efficacy analysis were carried out for the subjects eligible for the second phase of the study with at least one efficacy measurement in this phase.

Results and Demographics

In total, 409 patients were randomized to intermittent (degarelix, n = 177) or continuous treatment (degarelix, n = 50; leuprolide, n = 182). Baseline characteristics are shown in **Table 1**. Of 403 patients who initiated treatment, 25 (6%) patients had PSA >2.0 ng/mL at month 7 and were ineligible to enter the second phase of the study (**Figure 1**). An additional 50 patients discontinued before the seventh month, 328 patients entered the second phase, and 301 (74%) patients completed the trial (**Figure 1**). Overall, 37 patients discontinued due to AEs; the other main reasons for patients not completing the trial are shown in Figure 1.

Response Analysis: The response rate was similar between the intermittent arm (100%; 95% CI, 97.3–100.0) and the combined continuous arms (98.4%, 95% CI; 95.5–99.7; $P = 0.268$) (**Figure 2a**). The lower CI limit for the comparison of intermittent vs combined continuous arms was –0.19%; and therefore the threshold for noninferiority was met. Time to PSA >4.0 ng/mL was similar between the intermittent arm and the combined continuous arms ($P = 0.4758$). Time to PSA >4.0 ng/mL was not different between the intermittent arm and either continuous degarelix or leuprolide (**Figure 2b**). At month 14, no patients in the intermittent arm and 3 (1.6%) in the combined continuous arms had PSA >4 ng/mL (1 [2.4%] and 2 [1.3%] patients in the continuous degarelix and leuprolide arms, respectively; **Figure 2a**). In the intermittent arm, 35 (26%) patients restarted degarelix before month 14 for PSA >2 ng/mL.

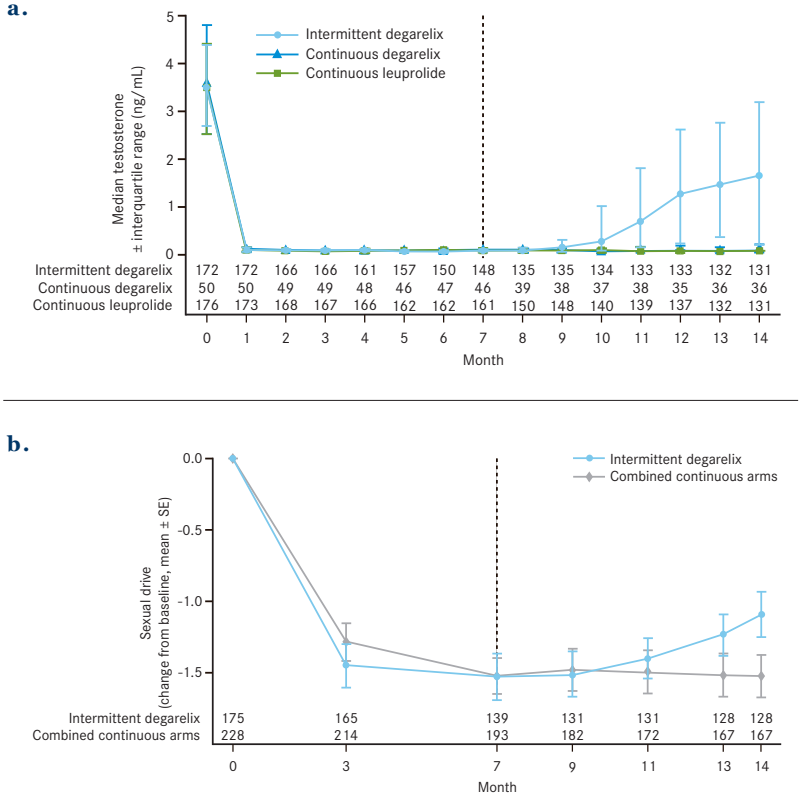
During months 7 to 14, 38 (28%) patients in the intermittent arm had PSA >2 ng/mL compared with 3 (6%) and 8 (5%) patients in the continuous degarelix and leuprolide arms, respectively ($P < 0.001$). Castration resistance occurred in 3 (2%) patients in the intermittent arm prior to month 7, 1 (2%) patient in the continuous degarelix arm between month 7 and 14, and no patients in the continuous leuprolide arm.

Testosterone Levels: Testosterone suppression was similar across study arms after treatment initiation. Median testosterone levels at month 3 were 0.07 ng/mL (range 0.02–0.31 ng/mL), 0.06 ng/

mL (range 0.02–0.22 ng/mL), and 0.08 ng/mL (range 0.02–0.38 ng/mL) in the intermittent and continuous degarelix and leuprolide arms, respectively. Testosterone values were significantly higher in the intermittent arm during months 9 to 14 when patients were off therapy (P <0.05 at each monthly measurement) (**Figure 3a**). At month 14, median testosterone was 1.65 ng/mL (range 0.015–16.2) in the intermittent arm, 0.075 ng/mL (range 0.015 – 0.94) in the continuous degarelix arm, and 0.07 ng/mL (range 0.015 – 0.25) in the continuous leuprolide arm.

Testosterone levels >0.5 ng/mL occurred in 116 (85%) intermittent-arm patients after a median of 112 days (95% CI, 112–140) from the cessation of degarelix (28 days after the last dose). The probability of testosterone >0.5 ng/mL was higher for patients aged <65 years (P = 0.0135). There were no differences in time to testosterone >0.5 ng/mL in the intermittent arm by disease stage, baseline PSA level, and PSA level at month 7 (P = 0.077, 0.506, and 0.384, respectively). Increase in testosterone to normal levels (>1.5 ng/mL) occurred in 94 (69%) intermittent-arm patients (median 168 days, 95% CI 140–168 days) and 0 (0%) and 1 (<1%) in the continuous degarelix and leuprolide arms, respectively. After 14 months, the median testosterone levels in men in the intermittent arm who had reached normal levels was 2.67 ng/mL (range 0.015 – 16.2).

FIGURE 3.



Median testosterone values (± interquartile range) for intermittent degarelix, continuous degarelix and continuous leuprolide treatment arms (a) and change from baseline in sexual drive (± standard error) for intermittent degarelix patients and the combined continuous treatment patients (b) over the entire course of the study.

Quality of Life: Sexual drive as measured in the SFI was improved at month 14 in patients in the intermittent arm versus those on continuous degarelix or leuprolide therapy (P = 0.027) (**Figure 3b**). In the intermittent arm, men with normal SFI scores at baseline were more likely to have significant increases in total SFI score (P = 0.034), sexual drive (P = 0.005), and erection (P = 0.010) while off treatment than than those on continuous degarelix and leuprolide arms with normal SFI scores at baseline.

Safety: Treatment emergent AEs were reported for 159 (91%) intermittent patients and 47 (94%) and 158 (89%) of patients in the continuous degarelix and continuous leuprolide arms, respectively (Table 2). The most frequently reported AE was hot flashes in 87 (50%), 26 (52%), and 110 (62%) of patients in the intermittent degarelix, continuous degarelix, and continuous leuprolide arms, respectively. Injection site reactions were reported by 58% and 66% of intermittent and continuous degarelix patients, respectively, and by 12% of patients in the continuous leuprolide arm. Injection site reactions were mild to moderate (grade 1–2) except 1 patient with grade 4 injection site erythema, induration, and pain (continuous degarelix arm).

The type and frequency of AEs during the first 7 months and months 7 to 14 of the study were similar. Grade 3 AEs were reported for 26 (15%), 6 (12%), and 18 (10%) patients in the intermittent degarelix, continuous degarelix, and continuous leuprolide arms, respectively (Table 2). There were 4 deaths (2 patients each in the intermittent degarelix and continuous leuprolide arms), none of which were considered related to study treatment or prostate cancer. Overall, 37 patients discontinued therapy due to treatment-related AEs (grades 1–3); 14 (8%), 5 (10%), and 18 (10%) patients from the intermittent degarelix, continuous degarelix, and continuous leuprolide arms, respectively (Table 2). The frequency, type, and grade of AEs leading to discontinuation was similar across treatment arms.

Discussion

These data suggest that intermittent use of degarelix as defined in this trial is non-inferior to continuous treatment with either degarelix or leuprolide with regard to maintenance of PSA ≤4

ng/mL at month 14. In the continuous treatment arms, rising PSA during months 7 to 14 may signal early castration resistant prostate cancer (CRPC). In contrast, rising PSA in the intermittent arm while off treatment was associated with increasing testosterone levels. As all patients in the intermittent arm who resumed ADT had a fall in PSA, there was no indication of early CRPC in this arm. This did not occur in any patients confirming that, despite a rise in PSA, these patients were not yet castration resistant. The treatment cycle length and PSA parameters (start intermittent phase if PSA ≤4 ng/mL and restart ADT when PSA >2 ng/mL) of this study are broadly similar to those used in other randomized trials of IAD versus CAD. Induction therapy is typically 6 to 8 months and the off-treatment period is initiated if PSA reaches <0.5 to <10 ng/mL (or a predefined percentage reduction from baseline).[15] Reintroduction of ADT in previous trials was triggered by PSA reaching either 10 or 20 ng/mL (or exceeding baseline)[7,8] or >4 ng/mL in the previous single-arm trial of degarelix in the intermittent treatment setting.[12]

Following discontinuation, the short half-life of degarelix[11] appears to allow a rapid testosterone increase to above castrate levels. After 7 months off degarelix, testosterone levels reached normal (1.5 ng/mL or 5.21 nmol/L) in 69% of patients, with a median level of 2.67 ng/mL. The data reported here are similar to those from a recent uncontrolled, open-label European-based study of degarelix.[12] In the first off-treatment period, the median time to testosterone >0.5 ng/mL was 112 days and time to PSA >4 ng/mL, 392 days.

Direct comparison with other trials is challenging due to differences in patient characteristics, treatments, and reporting parameters. However, the PR-7 study reported that, after 8 months of ADT with an LHRH analog, testosterone returned to baseline (>1.45 ng/mL or 5 nmol/L) in 79% of patients within 24 months of stopping ADT.[7] It could be speculated that an intermittent regimen with degarelix may allow a more rapid increase in testosterone that, in turn, may translate into more rapid improvement of side effects related to testosterone suppression. A comparison trial would be necessary to confirm this possibility.

In the current study, increased mean testosterone levels with intermittent therapy were associated with statistically higher sexual drive at month 14 compared with patients on continuous ADT. Patients with normal sexual function before initiating ADT had greater SFI improvements once testosterone levels increased, and there is a possibility these patients may benefit most from the potential sexual function improvements associated with IAD therapy. No other robust improvements in QoL for patients stopping treatment were found, which may partly be due to weaknesses of the QoL instruments for such assessments. Benefits in QoL with IAD for individual patients may depend on treatment cycle, testosterone status, and age.[7,4]

Administration of degarelix or leuprolide for up to 14 months was well tolerated. There was a higher rate of injection site reactions associated with the subcutaneous administration of degarelix compared with intramuscular injection of leuprolide. Injection site reactions were generally mild in nature and mostly reported following the first dose, consistent with results of previous studies.[8] The distinct different mechanism of LHRH agonists versus GnRH antagonists may be of relevance for the safety profile. Recently, LHRH agonist therapy has been associated with an increased risk of cardiovascular events in men with a history of cardiovascular disease[15] and of acute kidney injury in men with newly diagnosed nonmetastatic prostate cancer.[16] Interestingly, the same mechanism has been hypothesized to explain both these effects: GnRH receptor-mediated activation of T lymphocytes and cytokine secretion promoting subsequent inflammation and atherosclerotic plaque rupture.[16,17] Alternatively, GnRH antagonists or orchiectomy would not activate these inflammatory pathways, possibly explaining differences in the AEs associated with these different methods of androgen deprivation.[16,18]

Limitations of this study include the proportion of patients with an unclassifiable disease stage (due to limited imaging work-up at baseline) and following patients for only 14 months. As subjects in the intermittent group were treated if their PSA exceeded 2.0 ng/mL while off treatment, it is not possible to conclude whether men in the intermittent arm would have experienced PSA >4.0 ng/mL during the study term if left untreated. Also, 14 months may be insufficient time to assess the development of castration resistant disease (2 PSA measurements of >4 ng/mL while receiving ADT) in the intermittent arm due to the inherent delay caused by the off-treatment period.

Conclusions

ADT is associated with a number of AEs, some of which may be alleviated by intermittent treatment. In this trial, intermittent degarelix treatment was noninferior to CAD in terms of PSA control at 14 months, indicating degarelix is a viable therapeutic option in the intermittent setting. The potential clinical relevance of the difference in mechanism of action between a GnRH antagonist and LHRH agonists in this setting, for example, in patients at risk of cardiovascular disease, requires longer-term randomized controlled trials.

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