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ARTICLE

FSH suppression and tumour control in patients with prostate cancer during androgen deprivation with a GnRH agonist or antagonist

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ABSTRACT

Background: Gonadotropin releasing hormone (GnRH) antagonists suppress follicle-stimulating hormone (FSH) to lower levels than GnRH agonists. This may partially explain the differences between these agents on prostate cancer outcomes. In this post-hoc analysis, FSH and prostate specific antigen (PSA) responses and the impact of cross-over from leuprolide to degarelix were evaluated from a 1-year comparative study (CS21) and its extension study (CS21A).

Materials and methods: Overall, 610 patients were enrolled in CS21, wherein PSA and FSH levels were evaluated monthly. CS21A evaluated 386 patients, including those previously treated with degarelix ($n = 251$) who continued to receive degarelix, and those previously treated with leuprolide ($n = 135$) who crossed-over to receive degarelix. PSA and FSH levels were evaluated in CS21A for 3 months after cross-over. The associations between measurements were assessed using Spearman's correlation coefficient. The impact of class variables on FSH suppression were evaluated using Analysis of Variance.

Results: Rapid PSA and FSH suppression was observed and maintained in the degarelix arm (CS21 and CS21A), while patients on leuprolide experienced rising PSA during CS21. Patients crossed-over from leuprolide to degarelix achieved a suppression of FSH and a significant PSA decrease. PSA and FSH levels were significantly ($p < .05$) correlated at months 1, 3, 6, 12 and 13 in the degarelix arm.

Conclusions: Significant FSH suppression with GnRH antagonists may explain its advantage over GnRH agonists in terms of better prostate cancer control. The effect of profound FSH suppression is analogous to the need for profound testosterone suppression for tumor control.

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KEYWORDS
Degarelix; follicle stimulating hormone; leuprolide; prostate-specific antigen; prostate cancer

Introduction

Follicle stimulating hormone (FSH) may play a potential role in the initial development and progression of prostate cancer [1–3], as well as the time to castrate-resistant disease [2]. Evidence from pre-clinical studies show that FSH supplementation increase the growth of PC-3 prostate cell xenograft in gonadectomized mice [4]. This is because FSH is an endogenous product of the prostate tissue and it has been observed that FSH receptors are located and expressed by the endothelial cell lines in most of the tumour, including the prostate [5,6]. There is no evidence, however, that there are active FSH receptors on the prostate cancer cells [6].

Gonadotropin releasing hormone (GnRH) agonists induce an initial surge in testosterone level by stimulating the release of FSH and luteinizing hormone (LH), thus causing clinical flare in some patients with advanced stage disease. This is the reason for administration of anti-androgen, which is recommended during initial weeks of treatment with GnRH agonists. As the flare or surge is not observed with GnRH antagonists, it elicits a rapid and sustained suppression of testosterone to castrate levels [7–9]. Over and above, GnRH antagonists cause a rapid and profound FSH suppression that does not occur with GnRH agonists [10–12], suggesting a better prognosis with antagonists [3]. Pre-clinical studies in an androgen-insensitive model shows that degarelix elicit a tumor suppressing response by suppressing gonadotropins (FSH) as well as androgens (testosterone) [6]. It is, therefore, of interest to evaluate the impact of GnRH agonists and antagonists on FSH and prostate specific antigen (PSA) levels during the course of treatment, and also when patients cross-over from one ADT to another, especially in terms of disease prognosis.

Here, we present the results from a descriptive analysis of previous phase III studies, CS21 [9] and CS21A [1,13] that included patients with adenocarcinoma of the prostate (any stage). This analysis focuses on the impact of treatment with

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Supplemental data for this article can be accessed here.

GnRH agonists and antagonists on FSH levels, and relates FSH suppression to PSA suppression in patients with prostate cancer.

Materials and methods

Study design and population

Methodologies of the 1-year, phase 3, randomized, open-label study (CS21, NCT00295750) and its extension study (CS21A, NCT00451958) have been published previously [9,13]. The present analysis included 1-year data from CS21, and 3-month data following treatment cross-over in the extension study (Supplementary Figure 1). The CS21 study included 610 patients who were randomized to degarelix ($n = 409$, 240 mg in the first month, followed by 80 mg or 160 mg; subcutaneous injection) or GnRH agonist leuprolide ($n = 201$, 7.5 mg intra-muscular injection) for 13 months. A total of 386 patients completing CS21 were enrolled in the extension study CS21A, wherein patients previously treated with degarelix ($n = 251$) continued to receive the same monthly maintenance dose of 80 or 160 mg, while patients previously treated with leuprolide ($n = 135$) were re-randomized (1:1) to receive degarelix (starting dose of 240 mg followed by a monthly maintenance dose of 80 or 160 mg) for at least 1 year.

The population in this post-hoc analysis included the full analysis set population from CS21, as in the original treatment arms (degarelix [$n = 409$] and leuprolide [$n = 201$]), and all patients from CS21A, as in the original treatment arms (cross-over [$n = 135$] and continued degarelix [$n = 251$]).

Analysis objectives and endpoints

This analysis had two objectives. First, to assess the comparative effect of a GnRH agonist and antagonist on FSH levels, and the impact of FSH levels on prostate cancer prognosis. For this, the study evaluated the correlations between ADT and changes in FSH, PSA, and testosterone at months 1, 3, 6, 9, 12, and 13. Additional evaluations included the factors predicting percentage suppression in FSH at month 1, i.e. Gleason scores; prostate cancer stage at enrollment; Eastern Cooperative Oncology Group (ECOG) score; age; baseline body mass index (BMI); log baseline

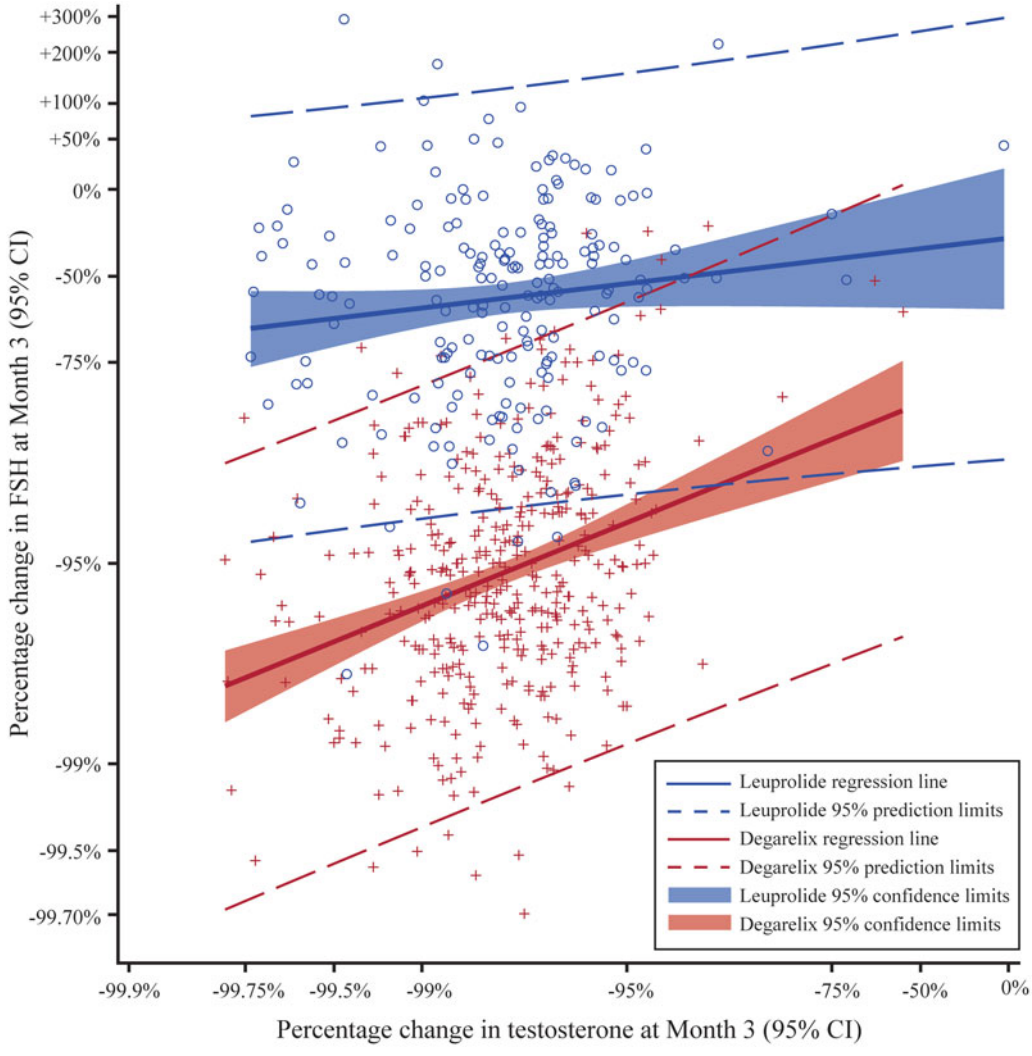

Figure 1. Percentage change in FSH and testosterone at month 3. CI: Confidence interval; FSH: Follicle stimulating hormone.

values for FSH, PSA and testosterone; and percentage change in testosterone at month 1. Second, to assess the impact of treatment cross-over (from GnRH agonist to antagonist) on FSH and PSA levels. For this, the absolute change in PSA levels from baseline (month 0) to month 1 up to month 16, correlation between FSH suppression at months 13 and 16 and residual FSH level at month 13, correlation between PSA and FSH levels at months 13 and 16 were determined in the cross-over and continued degarelix arms. PSA, FSH, testosterone and LH levels were noted at the end of every month, up to 16 months (12 months in CS21 and 4 months in CS21A).

Statistical analysis

Laboratory data were presented as absolute values at various time points and absolute change from baseline and percentage change from baseline at various time points were calculated. Measurements were log transformed to normality when appropriate, with an offset of 100% for the percentage change. Half of the lowest non-zero values were applied prior to log transformation for values of PSA and LH recorded as zero. Associations between measurements were assessed by Spearman's correlation coefficient. Impact of class variables on FSH suppression were evaluated using Analysis of Variance (ANOVA); 95% confidence intervals were

Table 1. Regression analysis for FSH and PSA.

	Treatment group					
	Leuprolide			Degarelix		
Period	*n*	Correlation of log-transformed values (SE)	*p*-value	*n*	Correlation of log-transformed values (SE)	*p*-value
Month 1	196	0.063 (0.084)	0.4565	403	0.132 (0.054)	.0158
Month 3	191	−0.108 (0.153)	0.4797	387	0.291 (0.088)	.0010
Month 6	185	0.314 (0.208)	0.1319	376	0.358 (0.116)	.0022
Month 9	181	0.434 (0.260)	0.0969	358	0.226 (0.114)	.0932
Month 12	172	−0.013 (0.113)	0.9050	332	0.396 (0.147)	.0073
Month 13	171	−0.150 (0.339)	0.6590	329	0.528 (0.162)	.0013

The data presents the correlation of FSH-suppression and PSA suppression in the two treatment groups at different time-points.
FSH: Follicle stimulating hormone; *n*: Number of patients; PSA: Prostate specific antigen; SE: Standard error.

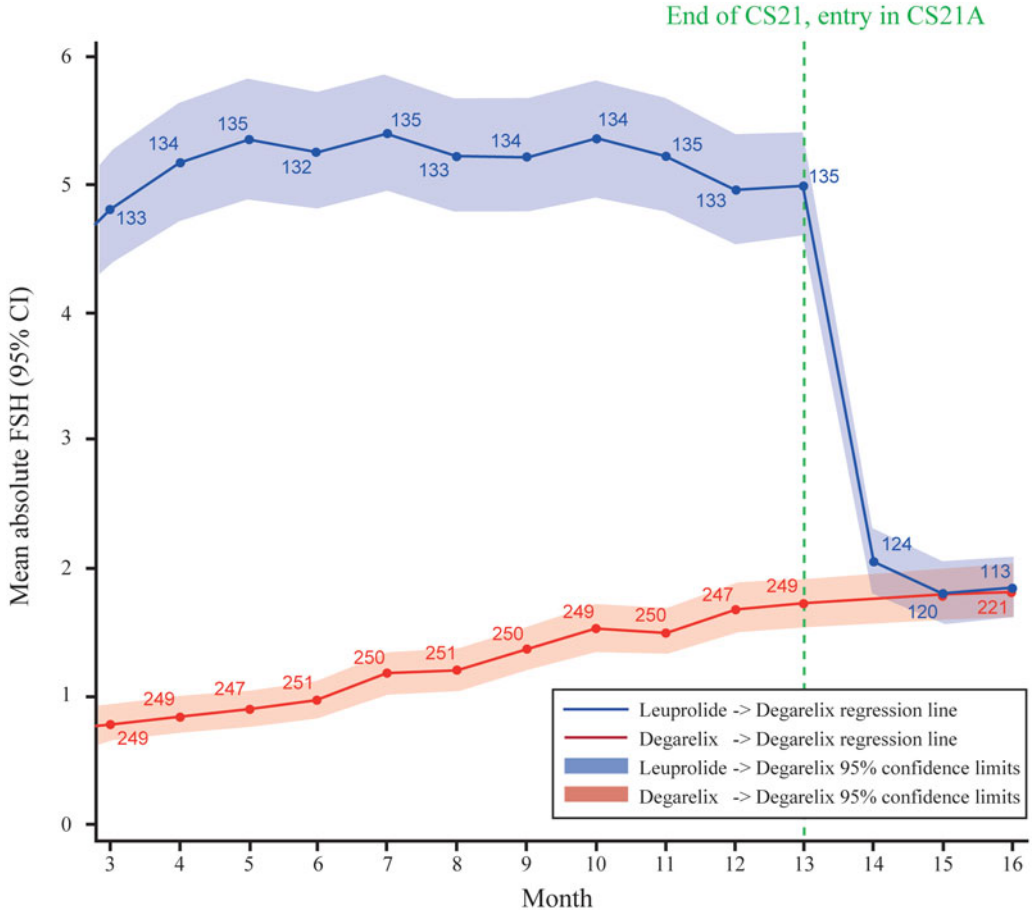

Figure 2. Absolute FSH levels following cross-over from leuprolide to degarelix (months 13–16). CI: Confidence interval; FSH: Follicle stimulating hormone.

reported. Wilcoxon rank sum test was used to compare PSA levels between the cross-over and continued degarelix arms. Wilcoxon signed rank test was used to compare PSA levels at different time points in the cross-over arm. The statistical significance level was set at 0.05 (two-sided).

Results

The baseline and disease characteristics of patients enrolled in CS21 study ($n = 610$) are presented in Supplementary Table 1. Disposition of patients continuing in CS21A study ($n = 386$) is presented in Supplementary Table 2.

Effect of GnRH agonist and antagonist therapy, and treatment cross-over on FSH and PSA levels

For a similar percentage suppression in testosterone, degarelix was associated with a significantly ($p = 0.0025$) greater percentage suppression in FSH versus leuprolide as analysed at month 3 (Figure 1). Additionally, the percentage suppression in FSH was positively and significantly correlated with percentage suppression in PSA for the degarelix arm, at all time-points except month 9. No such correlation was found in the leuprolide arm (Table 1).

Prior to cross-over, patients receiving leuprolide had mean FSH levels between 4.80 and 4.99 international units/liter (IU/L) from month 3 to month 13. Following cross-over to degarelix at month 13, FSH was rapidly suppressed by month 14 (2.05 IU/L), which was sustained up to month 16 (1.85 IU/L) (Figure 2). Overall, FSH levels showed an average suppression of 40% following the cross-over. In the continued degarelix arm, the mean FSH levels remained low (<2 IU/L) throughout the first 3 months of the extension phase, although FSH levels showed a small increase over the whole 15-month study period (Figure 2). The magnitude of FSH suppression was strongly and inversely related to the residual FSH level present in the patients at the time of cross-over (correlation coefficient = –0.852) (Figure 3). It was also seen that the FSH levels in cross-over patients fell to the 1-year FSH level of the patients initially treated with degarelix.

There was a small but gradual increase in mean PSA levels from month 3 to month 13 in both leuprolide and degarelix arms, however, by month 13 there was a significant difference in PSA levels between the two arms ($p = .0495$). Following cross-over at month 13, there was a rapid

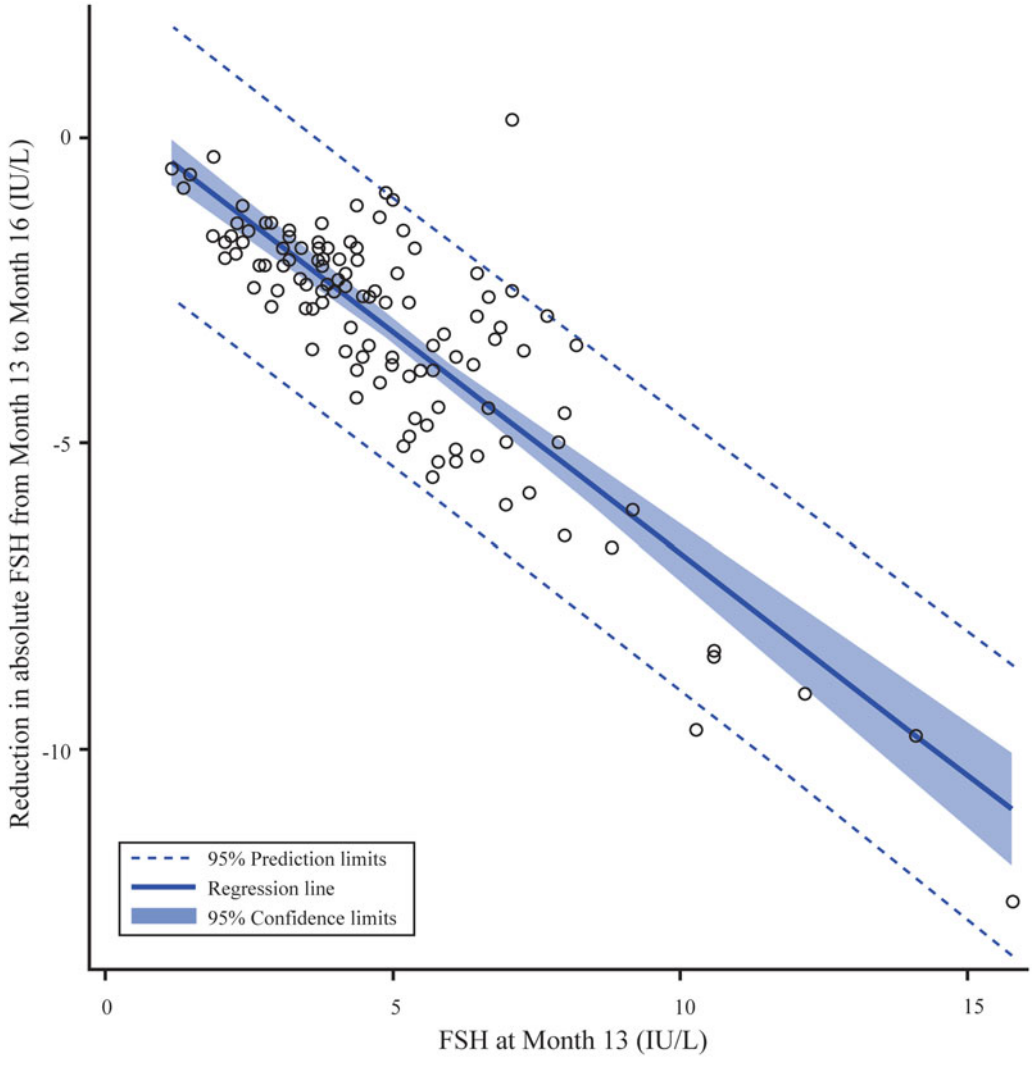

Figure 3. Correlation between residual FSH at month 13 and further FSH suppression between months 13 and 16. FSH: Follicle stimulating hormone.

suppression in PSA levels at month 14 (40.52 ng/mL) and this difference was statistically significant ($p < .001$). The PSA levels again gradually increased at month 16 (44.89 ng/mL) in the cross-over arm (Figure 4).

For patients in the continuous degarelix arm, the relationship between log (percentage change in PSA +100%) and log (percentage change in FSH +100%) was significant at month 13 ($p = .0022$) and month 16 ($p = .0413$) (Figure 5). On the other hand, log (percentage change in PSA +100%) and log (percentage change in FSH +100%) was not significant at month 13 ($p = .3209$) or month 16 ($p = .3624$) for the cross-over patients (Figure 6).

Factors affecting suppression of FSH during ADT

To understand the impact of demographic and clinical characteristics on FSH suppression, patients in each treatment arm were sub-grouped according to the degree of FSH suppression (strong, medium and weak) at month 1 (Table 2). FSH suppression seemed to be impacted by age as well as BMI. Older patients (with higher baseline FSH levels) had a stronger percentage FSH suppression versus younger patients in both the treatment arms at month 1, and the difference was statistically significant between the three FSH suppression sub-groups (degarelix, $p = .0226$; leuprolide, $p = .0005$). In the degarelix arm, higher baseline testosterone levels and greater percentage testosterone change from baseline to month 1 was associated with a greater FSH suppression at month 1 and the difference was statistically significant between the three FSH suppression sub-groups ($p < .0001$). In the leuprolide arm, baseline testosterone levels did not seem to affect FSH suppression ($p = .7580$). In both the treatment arms, there was sustained FSH suppression in each of the three FSH suppression sub-groups throughout the 13 months treatment period (Figure 7).

Discussion

This analysis of the phase 3 clinical trials evaluated FSH suppression and the factors that may predict FSH suppression during the course of 1 year treatment with degarelix and the subsequent cross-over from leuprolide to degarelix. Overall, the results showed that administration of degarelix versus leuprolide resulted in a rapid and sustained FSH suppression similar to that for testosterone. Additionally, cross-over of the patients from leuprolide to degarelix showed benefit in terms of FSH suppression and PSA reduction.

This analysis demonstrated that, despite a similar percentage suppression in testosterone by leuprolide and degarelix, the latter provided significantly greater FSH suppression than the former. Importantly, FSH suppression was positively and significantly correlated with percentage PSA suppression in

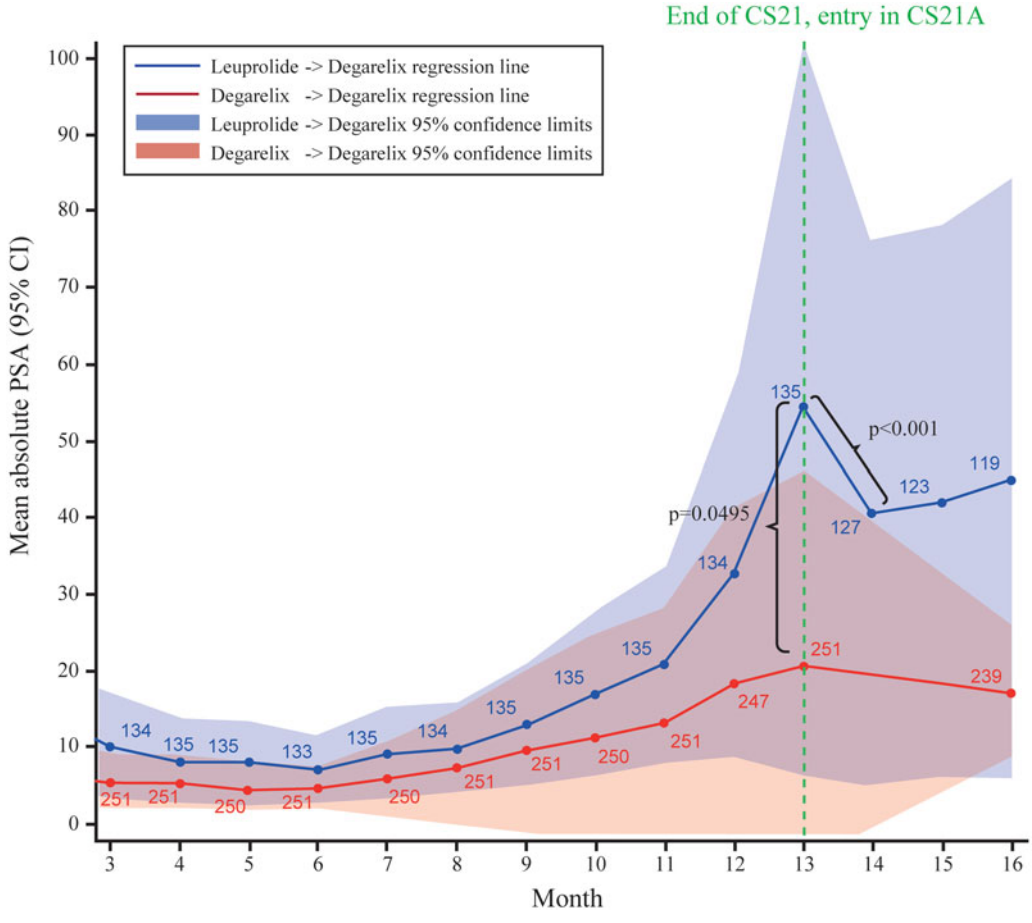

Figure 4. Absolute PSA levels (months 3–16). CI: Confidence interval; PSA: Prostate specific antigen.

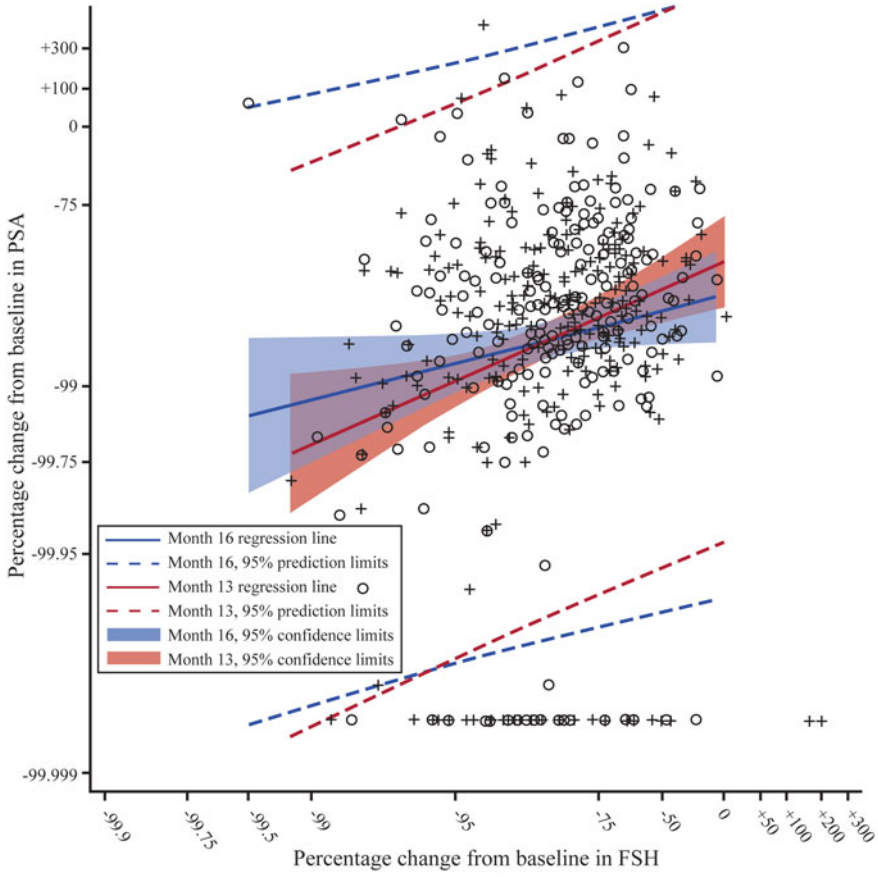

Figure 5. Correlation between PSA and FSH at months 13 and 16 in patients continuing on degarelix. FSH: Follicle stimulating hormone; PSA: Prostate specific antigen.

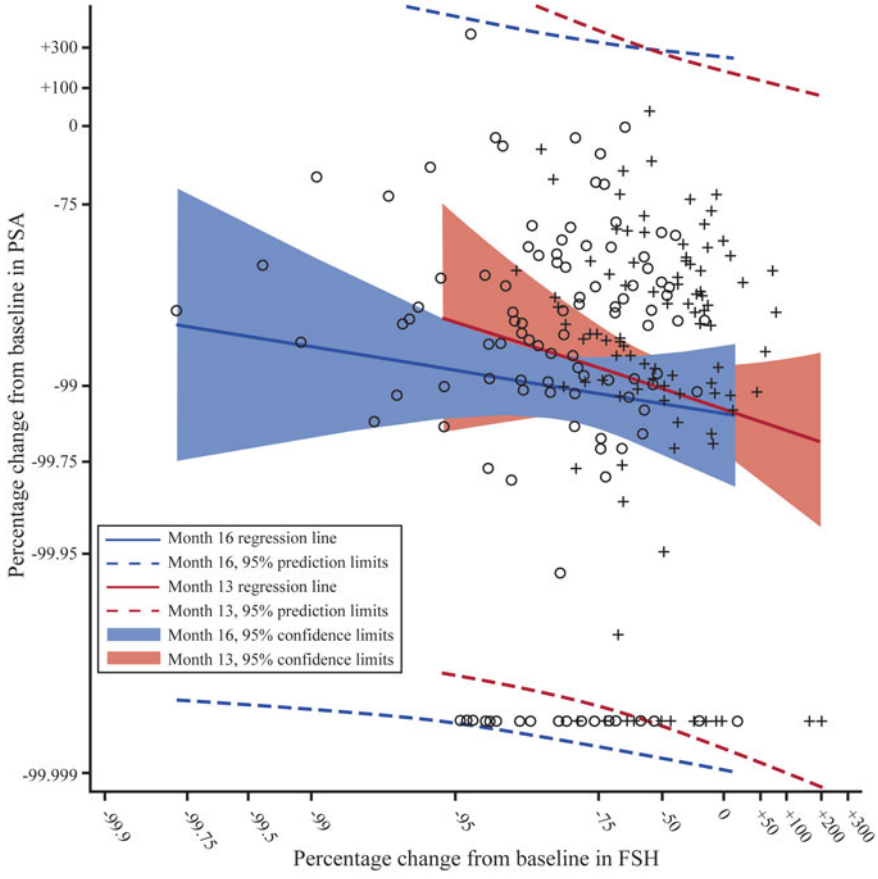

Figure 6. Correlation between PSA and FSH at months 13 and 16 in patients crossed-over from leuprolide to degarelix. FSH: Follicle stimulating hormone; PSA: Prostate specific antigen.

Table 2. Effect of demographics and clinical variables on percentage FSH suppression at month 1.

	Treatment group					
	Leuprolide			Degarelix		
	Strong FSH suppression (*n* = 65)	Medium FSH suppression (*n* = 66)	Weak FSH suppression (*n* = 65)	Strong FSH suppression (*n* = 136)	Medium FSH suppression (*n* = 133)	Weak FSH suppression (*n* = 134)
Age (years); Mean (SD)	65; 74.58 (8.85)	66; 73.45 (7.79)	65; 68.98 (8.85)	136; 73.29 (8.51)	133; 71.57 (7.53)	134; 70.55 (8.62)
ANOVA test (2-sided) *p*-value	0.0005			0.0226		
Gleason score, *n* (%)						
Missing	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.7)
2–4	8 (12.3)	11 (16.7)	5 (7.7)	17 (12.5)	9 (6.8)	13 (9.7)
5–6	19 (29.2)	22 (33.3)	22 (33.8)	46 (33.8)	49 (36.8)	39 (29.1)
7–10	38 (58.5)	32 (48.5)	38 (58.5)	73 (53.7)	74 (55.6)	81 (60.4)
Chi-square test* (2-sided) *p*-value	.5245			.3954		
Enrolment prostate cancer stage, *n* (%)						
Localized	21 (32.3)	20 (30.3)	21 (32.3)	41 (30.1)	44 (33.1)	42 (31.3)
Locally advanced	16 (24.6)	14 (21.2)	21 (32.3)	51 (37.5)	38 (28.6)	36 (26.9)
Metastatic	12 (18.5)	16 (24.2)	17 (26.2)	22 (16.2)	34 (25.6)	19 (14.2)
Not classifiable	16 (24.6)	16 (24.2)	6 (9.2)	22 (16.2)	17 (12.8)	37 (27.6)
Chi-square test* (2-sided) *p*-value	.8527			.1880		
ECOG score, *n* (%)						
0	46 (70.8)	50 (75.8)	49 (75.4)	98 (72.1)	96 (72.2)	104 (77.6)
1	14 (21.5)	13 (19.7)	13 (20.0)	26 (19.1)	32 (24.1)	25 (18.7)
2	5 (7.7)	3 (4.5)	3 (4.6)	12 (8.8)	5 (3.8)	5 (3.7)
Chi-square test* (2-sided) *p*-value	0.9175			0.2157		
Log Baseline BMI (kg/m^2), *n*; Mean (SD)	65; 3.26 (0.15)	66; 3.32 (0.14)	65; 3.28 (0.12)	136; 3.23 (0.15)	133; 3.27 (0.14)	134; 3.31 (0.14)
ANOVA test (2-sided) *p*-value	.0743			<.0001		
Log Baseline FSH (IU/L), *n*; Mean (SD)	63; 2.89 (0.73)	66; 2.18 (0.52)	65; 1.69 (0.54)	132; 2.35 (0.55)	132; 1.99 (0.87)	134; 2.11 (0.88)
ANOVA test (2-sided) *p*-value	<.0001			.0008		
Log Baseline PSA (ng/mL), *n*; Mean (SD)	64; 3.54 (1.95)	66; 3.05 (1.59)	65; 3.36 (1.69)	133; 3.43 (1.61)	132; 3.41 (1.64)	134; 3.02 (1.44)
ANOVA test (2-sided) *p*-value	.2793			.0518		
Log Baseline LH (IU/L), *n*; Mean (SD)	63; 2.32 (0.59)	66; 1.74 (0.57)	65; 1.48 (0.52)	133; 1.92 (0.57)	132; 1.73 (0.67)	134; 1.69 (0.61)
ANOVA test (2-sided) *p*-value	<.0001			.0050		
Log Baseline testosterone (ng/mL), *n*; Mean (SD)	64; 1.32 (0.44)	66; 1.35 (0.37)	65; 1.29 (0.47)	134; 1.47 (0.41)	133; 1.34 (0.41)	134; 1.23 (0.48)
ANOVA test (2-sided) *p*-value	.7580			<.0001		
Log (% change testosterone at Month 1 + 100%), *n*; Mean (SD)	65; 1.04 (0.63)	66; 1.13 (0.50)	65; 1.28 (0.58)	135; 0.55 (0.67)	133; 0.71 (0.60)	134; 1.04 (0.70)
ANOVA test (2-sided) *p*-value	.0506			<.0001		

*For Chi-square tests, missing categories and not classifiable are excluded from computations.
Strong FSH suppression: < –97.27 and < –82.65%; Medium FSH suppression: –97.27 to –94.11% and –82.65 to –65.55%; and Weak FSH suppression: ≥ –94.11 and ≥ –65.55% in degarelix and leuprolide groups, respectively.
ANOVA: Analysis of variance; BMI: Body mass index; ECOG: Eastern cooperative oncology group; FSH: Follicle stimulating hormone; IU: International unit; LH: Luteinizing hormone; N: Number of patients; n: number of patients analyzed; PSA: Prostate specific antigen; SD: Standard deviation.

the degarelix arm. This is clinically relevant, as PSA suppression to nadir levels is associated with an improved prognosis [14]. Therefore, improved tumor control could be related to testosterone as well as FSH suppression elicited by degarelix, which might delay the development of castrate-resistant prostate cancer (measured as PSA failure) versus agonists [15,16].

The above benefit was reiterated in the FDA mandated extension study where cross-over from leuprolide to degarelix was associated with a further suppression in FSH as well as PSA levels. Not only was the FSH suppression following cross-over at month 13 maintained up to month 16, but the higher FSH levels were mostly suppressed. The greater FSH suppression was reflected in greater PSA suppression for patients in the continuous degarelix arm. No such association was noted for the cross-over patients which could be due to a remaining depot effect of leuprolide. The data from CS21 also showed that PSA failure rate improved after switching from agonist to antagonist [13], supporting a potential role for FSH suppression in improved prostate cancer prognosis.

The FSH receptors have been demonstrated in tumor neo-vasculature [6]. A decrease in FSH may lead to the inhibition of neovascularization in the prostate tissue by reduced stimulation of FSH receptors. Profound FSH suppression would, thus, be analogous to a strong testosterone suppression by two different mechanisms to inhibit prostate cancer growth.

We also evaluated the demographic and clinical variables that may impact FSH suppression following treatment with antagonists or agonists. Treatment with degarelix was especially advantageous in terms of FSH suppression in patients with lower BMI, those with higher baseline testosterone levels, and those with greater testosterone suppression at month 1. Additionally, a trend towards greater benefit was noted in patients with higher baseline PSA levels. These factors, however, did not seem to impact the FSH suppression with leuprolide treatment. Other demographic and baseline clinical characteristics such as older age, higher baseline FSH and LH levels, apparently translated into greater FSH suppression with each of the treatments.

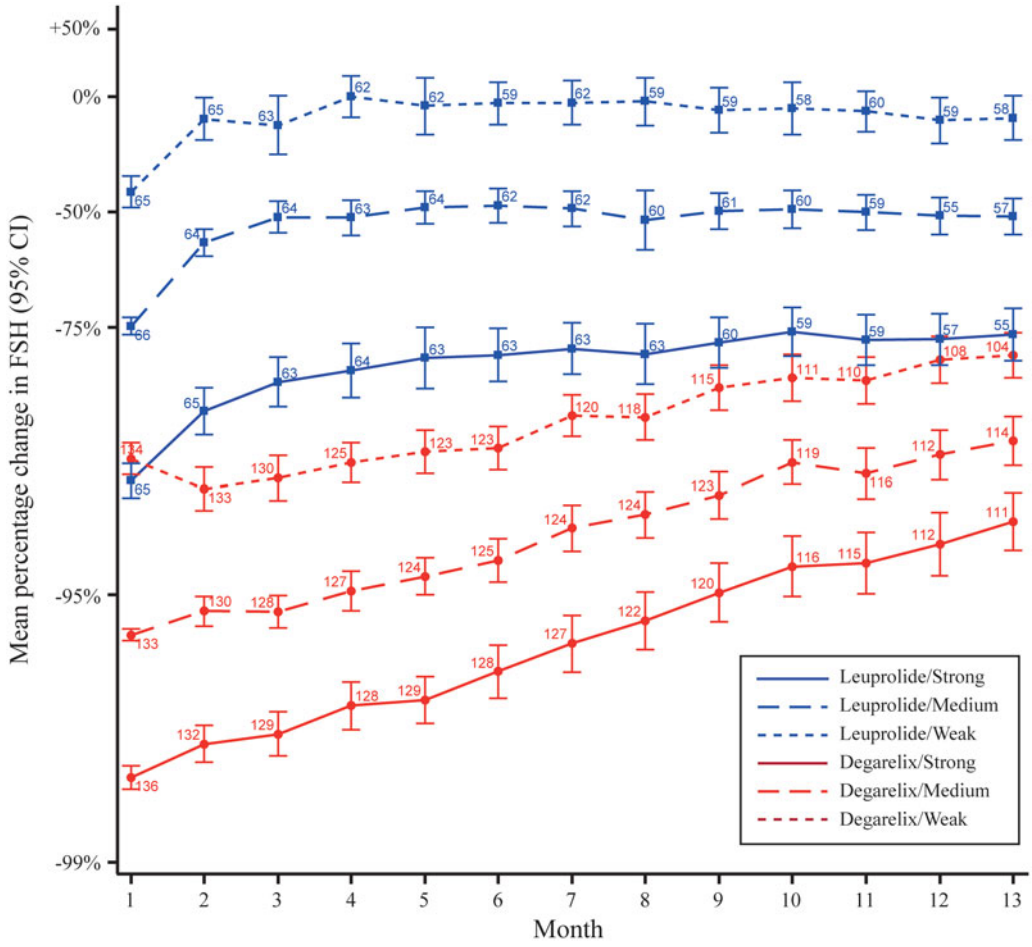

Figure 7. Average FSH levels during months 1–13 based on FSH suppression sub-groups. CI: Confidence interval; FSH: Follicle stimulating hormone.

The current analysis does have some limitations. First, the extension study design incorporated a cross-over from leuprolide to degarelix, but did not include a cross-over from degarelix to leuprolide. Thus, there was no direct comparator for the cross-over patients. Second, the measurement of FSH only continued for 3-months following cross-over.

Conclusions

Overall, our findings indicate that sustained FSH suppression to very low levels, or possibly high level FSH receptor blockade, could achieve better tumor control. Importantly, treatment efficacy, measured in terms of PSA suppression, was consistent with greater and sustained FSH suppression as demonstrated with degarelix treatment. Cross-over from leuprolide to degarelix and the associated FSH suppression was associated with suppression of PSA and improved PSA-PFS [12]. The superior FSH suppression with a GnRH antagonist may provide long-term benefits for patients with prostate cancer.

Geolocation information- Denmark

Disclosure of interest

No potential conflict of interest was reported by the authors.

Biographical note

Dr. Crawford is a distinguished Professor of Surgery, Urology, and Radiation Oncology, and head of the Section of Urologic Oncology at the University of Colorado Anschutz Medical Campus. Dr. Tombal is the Chairman of the Division of Urology and Professor of Urology at the Université catholique de Louvain (UCL), Cliniques universitaires Saint-Luc, Brussels, Belgium. Dr. Keane is professor and chairman of the Department of Urology at the Medical University of South Carolina in Charleston and specializes in managing prostate, bladder, and renal cancers. Dr. Boccardo is a professor at University of Genoa and director of the Academic Unit of Medical Oncology at Policlinico San Martino, Genoa. He is specialised in the management of urologic tumors. Dr. Miller is a urology specialist in Berlin. Dr. Shore is the Director, CPI at Carolina Urologic Research Center. Dr. Moul is a retired colonel and a noted researcher and clinician in the area of prostate cancer and is a urologic oncologist. Dr. Damber is a professor of urology in Sweden. Dr. Collette is the Associate Head of the Statistics Department and Head of the Independent Data Monitoring Committee (IDMC) Department at EORTC. Dr. Persson was a consultant to Ferring Pharmaceuticals.

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