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Degarelix monotherapy compared with luteinizing hormone-releasing hormone (LHRH) agonists plus anti-androgen flare protection in advanced prostate cancer: an analysis of two randomized controlled trials

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Abstract

Objectives: The objective of this study was to assess differences in efficacy outcomes between luteinizing hormone-releasing hormone (LHRH) agonist plus antiandrogen (AA) flare protection and monotherapy with the gonadotrophin-releasing hormone antagonist degarelix in patients with prostate cancer.

Methods: Data from 1455 patients were pooled from two prospective, phase III randomized 1-year clinical trials of degarelix *versus* LHRH agonist with or without AA. The AA bicalutamide was administered at the investigator's discretion. Adjusted hazard ratios (HRs) were calculated using a Cox proportional hazards regression model and a conditional logistic regression model was used for a case-control analysis of odds ratios (ORs).

Results: Patients received degarelix monotherapy (n = 972) or LHRH agonist (n = 483) of whom 57 also received AA. Overall, prostate-specific antigen progression-free survival (PSA PFS) was improved with degarelix *versus* LHRH agonist + AA (Cox proportional hazards regression model-adjusted HR for PSA PFS failure was 0.56 [95% confidence interval (CI) 0.33–0.97, p = 0.038]). To compensate for a higher proportion of patients with metastases, Gleason score 7–10, and PSA >20 ng/ml in the LHRH agonist + AA group, a case-control analysis using a conditional logistic regression model was utilized. This resulted in an OR for PSA PFS of 0.42 (95% CI 0.20–0.89; p = 0.023) in the overall population, and 0.35 (95% CI 0.13–0.96; p = 0.042) in patients with PSA >50 ng/ml at baseline, when treated with degarelix *versus* LHRH agonists + AA. There were a small number of deaths, 1.9% with degarelix and 7% with LHRH agonists + AA (case-control analysis OR = 0.37; p = 0.085).

Conclusions: Degarelix monotherapy produced a more favorable effect on PSA PFS outcomes than a LHRH agonist + AA flare protection therapy in patients with prostate cancer when a case-control analysis was used to compensate for differences between treatment groups.

Keywords: anti-androgen, degarelix, luteinizing hormone-releasing hormone agonist, prostate cancer, testosterone flare

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Introduction

Luteinizing hormone-releasing hormone (LHRH) agonist therapy has been used in advanced prostate cancer (PCa) for many years [Mottet *et al.* 2014]. However, these agents are associated with an initial testosterone surge which, in advanced disease, can produce a flare in symptoms and other metastatic manifestations [Thompson, 2001]. European Association of Urology (EAU) guidelines [Mottet *et al.* 2014] recommend concomitant anti-androgens (AAs) for selected patients in the initial 2 weeks of LHRH agonist

therapy to mitigate flare effects. However, while AAs decrease flare incidence, they do not prevent it in all men [Crawford *et al.* 1989; Lunglmayr, 1989; Du Plessis, 1991; Thorpe *et al.* 1996].

Any long-term impact of flare appears uncertain, with a lack of studies comparing long-term effects of flare protection *versus* no flare protection. Most available evidence relates to long-term use of AAs plus LHRH agonists in combined androgen blockade (CAB). Several studies have compared CAB using continuous AA plus LHRH agonist *versus* agonist monotherapy *without* AA flare protection [Crawford *et al.* 1989; Lunglmayr, 1989; Di Silverio *et al.* 1990; Du Plessis, 1991; Kotake *et al.* 1999; Noguchi *et al.* 2001]. While Crawford and colleagues showed that CAB achieved a significantly longer progression-free survival (PFS) and overall survival than LHRH agonist alone [Crawford *et al.* 1989], most of the other studies failed to show outcome benefits with CAB over agonist monotherapy. Four studies comparing CAB (LHRH agonist plus long-term AA) *versus* agonist 'monotherapy' *with* initial AA flare protection [Ferrari *et al.* 1993; Ferrari *et al.* 1996; Bono *et al.* 1998; De Voogt *et al.* 1998] also showed no difference in efficacy outcomes. However, the absence of prospective studies comparing initial AA flare protection *versus* no flare protection make it difficult to confirm the influence of initial flare protection on long-term outcomes.

Meta-analyses showed a small survival benefit for 5 years of treatment with CAB *versus* LHRH agonist monotherapy ± AA flare protection [Prostate Cancer Trialists' Collaborative Group, 2000; Samson *et al.* 2002]. A re-analysis of the Prostate Cancer Trialists' Group meta-analysis assessed the impact of disease flare by excluding trials without initial AA [Collette *et al.* 2001]. Analysis of 15 trials from the meta-analysis showed no significant survival benefit of CAB *versus* castration alone *with* initial AA flare protection. This may suggest a negative impact of disease flare on survival which does not occur when AA is given.

Gonadotrophin-releasing hormone (GnRH) antagonists have been developed, as an alternative to LHRH agonists to achieve effective long-term medical castration without the testosterone surge and associated flare risk. Unlike LHRH agonists, where the testosterone surge results from an initial intense receptor stimulation prior to downregulation/desensitization, GnRH antagonists directly block receptors, producing rapid testosterone suppression without an initial surge. The most extensively studied and widely available antagonist, degarelix, showed no evidence of testosterone surge or flare in clinical studies [Gittelman *et al.* 2008; Klotz *et al.* 2008; Van Poppel *et al.* 2008; Ozono *et al.* 2012].

Recently, pooled analyses of data from prospective randomized phase III trials of degarelix *versus* LHRH agonists have reported increased prostate-specific antigen (PSA) PFS and survival [Klotz *et al.* 2014]; here we focus on data from patients treated with an AA in addition to a LHRH agonist in the 1-year trials. In the pivotal phase III trial (CS21), degarelix was as effective as the LHRH agonist leuprolide (± AA) at maintaining low testosterone levels over 1 year [Klotz *et al.* 2008]. A more recent large phase III trial (CS35) compared the efficacy and safety of 3-month dose regimens of degarelix and the LHRH agonist goserelin (± AA) over 1 year [Tombal *et al.* 2012]. Using pooled data from these two trials, we compared the efficacy outcomes of degarelix monotherapy *versus* combined LHRH agonist plus AA in PCa.

Patients and methods

Study designs and patients

Data were pooled from two prospective, randomized open-label 1-year clinical trials (CS21 and CS35) comparing degarelix with LHRH agonist (with or without AA) in patients with PCa. Both trials were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Study protocols were approved by independent ethics committees and institutional review boards. All patients provided written informed consent.

Study CS21. The methodological details of study CS21 have been published [Klotz *et al.* 2008]. CS21 was a comparative study of degarelix *versus* leuprolide in patients (n = 610) with hormone-naïve adenocarcinoma of the prostate (any stage), a serum testosterone >1.5 ng/ml and a PSA >2 ng/ml, for whom endocrine treatment was indicated. Degarelix was administered as a monthly subcutaneous injection (240 mg for the first month followed by 12 maintenance doses of 80 or 160 mg). Leuprolide was administered as monthly intramuscular injections of 7.5 mg for 12 months. In the leuprolide group, the AA bicalutamide (50 mg once daily) was administered at the start

of treatment for flare protection at the investigator's discretion; of those receiving AA flare protection, the majority (86%) received bicalutamide for ⩽28 days.

Study CS35. This was a comparative study of 3-month formulations of degarelix *versus* goserelin in hormone-naïve patients (n = 848) with PCa requiring androgen deprivation therapy. Degarelix was administered at a starting dose of 240 mg followed by 4 maintenance doses of 480 mg at months 1, 4, 7 and 10. Goserelin was administered at a starting dose of 3.6 mg of the 1-month implant followed by 4 doses of 10.8 mg of the 3-month implants at months 1, 4, 7 and 10. Bicalutamide was administered at the investigator's discretion as flare protection at the start of the goserelin treatment for a maximum of 28 days [Tombal *et al.* 2012].

Statistical analyses

Patients in the LHRH agonist arm were considered to have received concomitant AA if treatment started in ⩽6 days of LHRH agonist treatment (n = 57). Two patients in the degarelix arm who received AA were excluded from the analysis. In total, 972 degarelix patients were included in the pooled analysis.

Median percentage change over time in testosterone and PSA for all patients is reported. Time to PSA PFS was defined as time to PSA failure or death, whichever was first. PSA failure was defined as 2 consecutive PSA increases of ⩾50% *versus* nadir and ⩾5 ng/ml on two consecutive measurements ⩾2 weeks apart.

Adjusted hazard ratios (HRs), 95% confidence intervals (CIs) and p values for PSA PFS failure were calculated using a Cox proportional hazards regression model. For analysis of all patients and patients with baseline PSA >20 ng/ml or >50 ng/ml, HRs were adjusted for baseline PSA (continuous), PCa stage and Gleason score; for estimates of mortality rates, age was an additional adjustment factor. To account for variations in risk factors across the patient population, a case-control analysis was performed using a conditional logistic regression model. Patients were matched according to baseline characteristics by stratifying by Gleason score (2–4, 5–6 and 7–10), disease stage (localized, locally advanced, metastatic and not classifiable) at enrolment and baseline PSA (⩽10, >10–20, >20–50 and >50 ng/ml).

Results

Patients

In the pooled CS21 and CS35 full analysis set populations (n = 1455), 972 patients received degarelix, 426 received LHRH agonist without AA, and 57 received LHRH agonist with AA. Baseline patient characteristics are summarized in Table 1. The LHRH agonist + AA group contained a higher proportion of patients with Gleason score 7–10, metastatic disease or baseline PSA >50 ng/ml compared with the degarelix group; baseline PSA was also higher in the LHRH agonist + AA group and these characteristics were used for baseline adjustments as well as stratification in the case-control analysis.

Testosterone

The median percentage change in testosterone, during 13 months of treatment, was similar for degarelix and LHRH agonist + AA groups (Figure 1a). After 1 month, median testosterone was reduced by >90% in both groups and remained suppressed over the 13-month study periods. Median testosterone levels at day 364 were 0.11 (0.02–4.19) ng/ml and 0.07 (0.02–0.19) ng/ml for degarelix and LHRH agonist + AA groups respectively.

PSA

In the overall patient population, a rapid initial median reduction in PSA (~75% in the first month) was observed in patients receiving degarelix and those receiving a LHRH agonist + AA (Figure 1b). PSA continued to fall in both groups and was suppressed around these low levels for the remainder of the study durations.

PSA PFS

The hazard ratio (HR) for PSA PFS failure for degarelix *versus* LHRH agonist + AA [adjusted for baseline PSA (continuous), PCa stage and Gleason score] was 0.56 (95% CI 0.33–0.97; p = 0.038). For the case-control analysis, only stratification levels with controls (did not fail PSA PFS criteria) and cases (PSA PFS failure) were included. This gave a total of 674 controls (637 and 37 treated with degarelix and LHRH agonist + AA, respectively) and 134 cases (119 and 15 treated with degarelix and LHRH + AA, respectively). When treated with degarelix compared with LHRH agonist + AA, there was a significantly lower odds

Table 1. Baseline patient characteristics for pooled CS21 and CS35 populations.

	Degarelix	GnRH agonist with AA	GnRH agonist without AA
n	972	57	426
Age, years			
Mean (SD)	71.9 (8.3)	71.7 (8.1)	71.6 (8.3)
Range	46–94	58–98	51–92
PSA, ng/ml			
Median (range)	19.4 (0.26 to 1.7 × 10^4)	22.2 (2.4 to 1.3 × 10^4)	18.3 (0.01 to 1.1 × 10^4)
PSA category (ng/ml), n (%)			
0–10	284 (29)	20 (35)	140 (33)
>10–20	213 (22)	7 (12)	85 (20)
>20–50	194 (20)	11 (19)	89 (21)
>50	279 (29)	19 (33)	112 (26)
Total	972 (100)	57 (100)	426 (100)
Testosterone (ng/ml)			
Median (range)	4.26 (0.07–14.5)	4.22 (1.52–9.03)	4.27 (0.07–13.2)
Gleason category, n (%)			
2–4	90 (9)	3 (5)	37 (9)
5–6	322 (33)	7 (12)	145 (34)
7–10	553 (57)	47 (82)	243 (57)
Total	965 (99)	57 (100)	425 (100)
PCa stage, n (%)			
Localized	293 (30)	13 (23)	140 (33)
Locally advanced	277 (28)	16 (28)	110 (26)
Metastatic	249 (26)	19 (33)	99 (23)
Not classifiable	153 (16)	9 (16)	77 (18)
Total	972 (100)	57 (100)	426 (100)

AA, antiandrogen; GnRH, gonadotrophin-releasing hormone; PCa, prostate cancer; PSA, prostate-specific antigen; SD, standard deviation.

ratio (OR) of PSA PFS failure for the overall population (OR = 0.42, 95% CI 0.20–0.89; $p = 0.023$) as well as for patients with baseline PSA >50 ng/ml (OR = 0.35, 95% CI 0.13–0.96; $p = 0.042$).

Survival

The Cox proportional hazards regression model-adjusted HR for overall mortality for degarelix *versus* LHRH agonist + AA for the all-patient cohort was 0.34 (95% CI 0.12–1.02; $p = 0.055$); adjusted for age, PCa stage, Gleason score and baseline PSA (continuous). The OR in the case-control analysis was 0.37 (95% CI 0.12–1.15; $p = 0.085$) (Figure 2).

Death occurred in 4 of 57 patients in the LHRH agonist + AA group and 18 of 972 patients in the degarelix group. Overall, only three patients were classified as having died from PCa, none of whom were in the LHRH agonist + AA group. The majority of deaths were classified as resulting from cardiovascular (CV) causes. The limited size of the LHRH agonist + AA group may restrict the detection of potential differences.

Discussion

EAU guidelines recommend AAs in the initial 2 weeks of LHRH agonist therapy to reduce clinical flare [Mottet *et al.* 2014]. However, our analysis suggests that 2 weeks of AA flare protection is associated with poorer outcomes than degarelix monotherapy. Thus, compared with LHRH agonist + AA, degarelix was associated with significantly higher PSA PFS in the overall population and in patients with baseline PSA >50 ng/ml.

Our pooled analyses showed rapid and profound testosterone suppression for both treatment groups. However, both studies showed an initial increase in testosterone with LHRH agonist + AA but not with degarelix [Tombal *et al.* 2012; Klotz *et al.* 2008]. GnRH antagonists also produce a greater and more persistent suppression of follicle-stimulating hormone (FSH) compared with LHRH agonists [McLeod *et al.* 2001; Trachtenberg *et al.* 2002; Klotz *et al.* 2008]. While the therapeutic advantage of persistent FSH suppression with antagonists remains to be established, several studies have linked FSH with PCa [Ben-Josef *et al.* 1999; Mariani *et al.* 2006; Heracek *et al.* 2007; Radu *et al.* 2010].

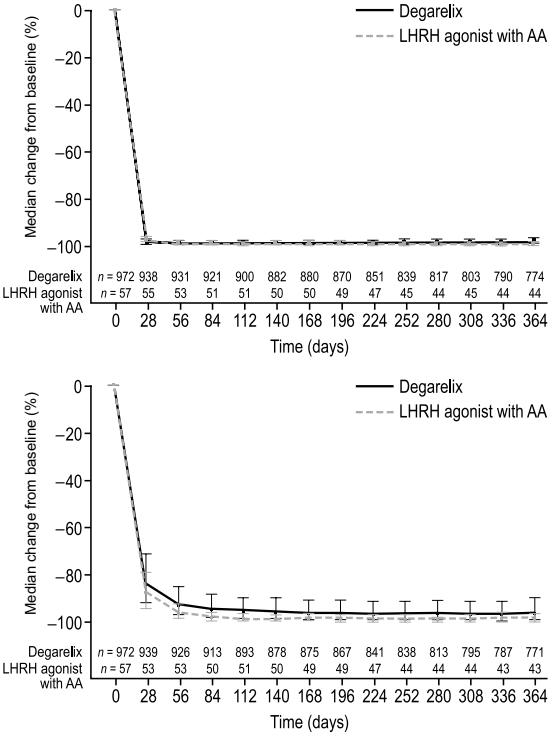

Figure 1. Median (±95% CI) percentage change in testosterone (a) and median PSA (± interquartile range) (b) over time for patients receiving degarelix *versus* LHRH agonist + anti-androgen.
AA, antiandrogen; CI, confidence interval; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

The current analysis showed that, with both treatments, PSA suppression for all patients was rapid and maintained at similarly low levels. Speed of PSA decline (PSA halflife) might be of prognostic significance. Some studies suggest that more rapid PSA reduction (shorter PSA halflife), is associated with improved progression and survival [Hanninen *et al.* 2009; Lin *et al.* 2009], although conflicting results have been reported [Park *et al.* 2009]. In CS21, the PSA halflife for degarelix was shorter than with leuprolide ± AA [Van Poppel and Klotz, 2012].

Our analysis showed a marked difference in baseline characteristics between treatment groups: the LHRH agonist + AA group had higher proportions of patients with Gleason score 7–10, metastatic disease or baseline PSA >50 ng/ml. These differences facilitate poorer prognosis, and less favorable outcomes, in the LHRH agonist + AA group. A case-control analysis was therefore used to stratify patients across treatment groups in terms of Gleason score, baseline PSA and PCa stage; conditional logistic regression allows investigation of the relationship between an outcome being an event (case) or not (control) with treatment (degarelix

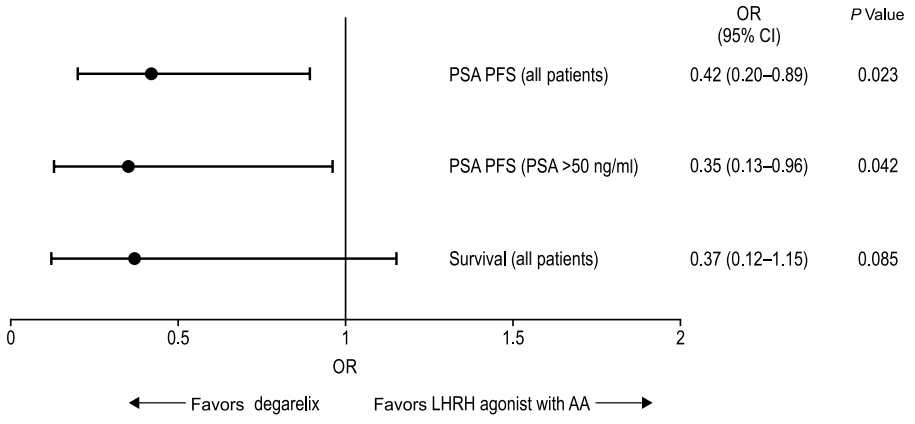

Figure 2. Forest plot showing OR ± 95% CI for PSA PFS and survival in the case-control analysis.
CI, confidence interval; OR, odds ratio; PSA PFS, prostate-specific antigen progression-free survival.

or LHRH + AA) as the only remaining variable to estimate.

In PCa, PSA recurrence often precedes clinically detectable recurrence by years and effective PSA control is associated with improved overall survival [Williams *et al.* 2004; Hussain *et al.* 2006; Hussain *et al.* 2009]. Any improvement in time to progression or death is clearly desirable and prolongation of PSA PFS by degarelix *versus* LHRH agonist + AA is likely to delay onset of castrate-resistant disease.

Baseline disease stage and pretreatment PSA are associated with PCa outcome [Stock and Stone, 1997; D'amico *et al.* 2007]. In patients with metastatic disease, estimates suggest >90% will progress to androgen independence within 18–24 months [Petrylak, 2005]. In study CS21, patients at highest risk of PSA failure were those with advanced disease or baseline PSA >20 ng/ml [Tombal *et al.* 2010]. In our analyses, adjusted HRs showed significantly higher PSA PFS for degarelix in patients with baseline PSA >50 ng/ml.

The current analysis did not indicate a difference in mortality risk between degarelix and LHRH agonist + AA; the low number of deaths did not allow a robust comparison. Recent data have reported an increased risk of diabetes and certain CV diseases with LHRH agonist treatment [Levine *et al.* 2010]. In contrast, a pooled analysis of clinical trial data showed that degarelix dose and treatment duration were not independently associated with CV disease events [Smith *et al.* 2011]. More recently, another pooled analysis of degarelix comparative trials has shown that, in patients with a history of CV disease, degarelix was associated with a significantly lower risk (>50%) of subsequent CV event or death over 1-year of treatment compared with LHRH agonists [Albertsen *et al.* 2014]. The majority of deaths in the current study were due to CV causes (only three PCa deaths occurred in the degarelix group), but a potential difference between treatment with degarelix and LHRH agonist + AA in terms of overall survival and CV-related death requires confirmation with larger studies.

Limitations of this pooled analysis include the *post hoc* nature of the analysis, follow up of 1 year and the differences between the groups in terms of patient numbers and baseline characteristics, particularly the higher proportion of patients with metastatic disease in the LHRH agonist + AA group at baseline. However, when adjusted for confounding baseline factors and matched by baseline characteristics in a case-control analysis, the data indicate better PSA PFS with degarelix monotherapy compared with AA flare protection added to LHRH agonist during the first year of treatment. Thus, flare avoidance in patients at risk of PSA failure (e.g. high baseline PSA or metastatic disease) can be better achieved with GnRH antagonist monotherapy than with LHRH agonist plus AA, especially when evidence indicates that testosterone surge and flare effects can still occur when AAs are added to LHRH agonist therapy [Crawford *et al.* 1989; Kuhn *et al.* 1989; Klotz *et al.* 2008].

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Conflict of interest statement

P.I., J.-E.D. and L.K. have received honoraria from Ferring Pharmaceuticals for attending advisory boards and/or scientific meetings. A.M. is an employee of Ferring Pharmaceuticals and B.-E.P. is a consultant to Ferring Pharmaceuticals.

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