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Title:

Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix

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Long-term Tolerability and Efficacy of Degarelix: 5-Year Results From a Phase III Extension Trial With a 1-Arm Crossover From Leuprolide to Degarelix

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OBJECTIVE	To demonstrate the safety and efficacy of up to 5 years of degarelix treatment and the effects of crossing over from leuprolide to degarelix in the extension phase of a phase III pivotal 1-year trial.
METHODS	Patients receiving degarelix who completed the 1-year trial continued on 80 mg (n = 125) or 160 mg (n = 126) maintenance doses. Patients who received leuprolide were rerandomized to degarelix 240/80 mg (n = 69) or 240/160 mg (n = 65). Safety and tolerability were assessed (primary end point), as well as testosterone and prostate-specific antigen levels and prostate-specific antigen progression-free survival (secondary end points).
RESULTS	Adverse event frequency was similar between both the groups. Adverse events included initial injection site reactions, hot flushes, and increased weight. Testosterone and prostate-specific antigen values during the extension study were similar to those seen during the 1-year trial in patients who continued on degarelix or crossed over from leuprolide. The prostate-specific antigen progression-free survival hazard rate was decreased significantly after the crossover in the leuprolide to degarelix group (from 0.20 to 0.09; $P = .002$), whereas in patients who continued on degarelix, the rate did not change significantly. In patients with baseline prostate-specific antigen >20 ng/mL, the same hazard rate change pattern was observed on crossover (from 0.38 to 0.19; $P = .019$).
CONCLUSION	Degarelix was well tolerated; no safety concerns were identified. The significant prostate-specific antigen progression-free survival benefit established for degarelix over leuprolide during year 1 remained consistent at 5 years. UROLOGY 83: 1122–1128, 2014. © 2014 Elsevier Inc.

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The gonadotropin-releasing hormone antagonist, degarelix, is approved for the treatment of advanced prostate cancer (PCa). (Degarelix was approved by the US Food and Drug Administration in December 2008 and by the European Medicine Agency in February 2009.)¹ The prospective comparative trial CS21 (ClinicalTrials.gov identifier NCT00295750) evaluated 2 maintenance doses of degarelix (80 and 160 mg) vs the luteinizing hormone-releasing hormone (LHRH) agonist leuprolide (7.5 mg) in patients with PCa.² Degarelix rapidly suppresses testosterone to castrate levels without the initial testosterone surge associated with LHRH agonists.³ The primary end point of cumulative probability of testosterone level ≤ 0.5 ng/mL from 28 to 364 days was 97.2% and 98.3% for the 80- and 160-mg maintenance degarelix doses, respectively, and degarelix was at least as effective as leuprolide at maintaining castrate levels of testosterone. Secondary end points demonstrated that after 28 days, serum levels of

prostate-specific antigen (PSA) and luteinizing hormone (LH) were similar between the treatment arms.² A subsequent analysis demonstrated a clinically significant decrease in the risk of PSA progression or death (PSA progression-free survival [PFS]) over 1 year in the degarelix group ($P = .05$).⁴ Levels of follicle-stimulating hormone (FSH) and, in patients with metastatic disease, serum alkaline phosphatase were suppressed to a greater degree in degarelix-treated patients.^{2,5}

Over the course of 1 year, both agents were well tolerated with flushing the most frequently reported adverse event (AE). More patients reported arthralgia and urinary tract infections with leuprolide, and injection-site reactions and chills were more frequent with degarelix; none of these AEs were considered serious. To investigate the long-term safety of degarelix, patients who successfully completed CS21 were offered the opportunity to enter the extension trial CS21A in which they continued to receive degarelix or crossed over from leuprolide to degarelix. The crossover was preplanned for all patients on leuprolide. The incidence of AEs at interim follow-up of the extension phase was similar to that seen in the first year.⁶ The incidence of injection-site reactions reported for leuprolide to degarelix crossover patients was as expected and presumably related to the subcutaneous route of degarelix administration.

LH and FSH levels were recorded for 3 months in CS21A. Patients who crossed over from leuprolide to degarelix demonstrated further FSH suppression during this time. At a median follow-up of 27.5 months, suppression of testosterone and PSA was maintained in patients continuing to receive degarelix and those who crossed over from leuprolide to degarelix.⁶ After crossing over from leuprolide to degarelix, the PSA PFS hazard rate improved significantly ($P = .003$). A similar significant improvement ($P = .043$) in the PSA PFS hazard rate was experienced by patients with baseline PSA level >20 ng/mL.⁶

We now report 5-year follow-up safety and efficacy data for patients who received degarelix 240/80 mg for up to 5 years or those who crossed over from leuprolide to degarelix after 1 year of treatment.

MATERIALS AND METHODS

The methodological details of the original 1-year, phase III, randomized, open-label trial (CS21) have been previously reported.² Patients completing 1 year of treatment in CS21 were eligible to enroll into the open-label, multicenter, 4-year extension study. Patients initially treated with degarelix continued with the same monthly maintenance dose (ie, 160 or 80 mg). Those who previously received leuprolide 7.5 mg were rerandomized (1:1) to receive a starting dose of degarelix 240 mg followed by monthly doses of 80 or 160 mg. On regulatory approval of degarelix 240/80 mg, patients receiving the 160-mg maintenance dose transferred to the approved maintenance dose. Patients received up to 5 years of degarelix treatment. The trial complied with the Declaration of Helsinki and was

approved by independent ethics committees or institutional review boards. Patients provided written informed consent.

The primary objective was to evaluate safety and tolerability during long-term treatment with degarelix. The secondary objective was to assess testosterone and PSA responses during long-term treatment with degarelix. Secondary objectives evaluating LH and FSH responses for up to 3 months from the time of crossover from leuprolide to degarelix have already been reported.⁶ Safety and tolerability were assessed by measuring AEs. For patients continuing on degarelix, data are shown for the approved degarelix 240/80 mg dose. Data on patients who crossed over from leuprolide to degarelix 240/80 and 240/160 mg (and subsequently to 80 mg) were pooled (leuprolide to degarelix group). The database was finalized in December 2011 after a median exposure to degarelix of 57.1 months (range, 12.8-72.4 months).

Serum testosterone and PSA levels were measured monthly for the first 3 months and then at 3-month intervals until the end of the extension phase. LH and FSH levels were measured for the first 3 months of the extension phase only. Analysis was performed at a central laboratory. PSA progression was defined as 2 consecutive PSA increases of $\geq 50\%$ vs nadir and ≥ 5 ng/mL on 2 consecutive measurements ≥ 2 weeks apart with the end point recorded on the date of the second measurement according to protocol CS21 criteria.

Time to PSA PFS was defined as time to PSA progression or death, whichever came first; PSA PFS was analyzed using the Kaplan-Meier method, in both the overall population and the subgroup of patients with baseline PSA level >20 ng/mL. PSA PFS hazard rates were calculated before and after crossover using a likelihood ratio-based procedure⁷ to test for a change in the hazard rate of the patient survival distribution, and statistical comparisons were made using the chi-square test. All analyses were performed and summary statistics calculated using SAS, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

In total, 386 patients continued into the extension study after the first year of treatment. For patients randomized to receive degarelix in CS21, 251 continued on the same monthly degarelix maintenance dose of 80 mg ($n = 125$) or 160 mg ($n = 126$). (For patients continuing on degarelix, data are reported only for the approved degarelix 240/80 mg dose, with the exception of AEs.) Of 172 leuprolide-treated patients completing CS21, 135 entered the extension trial and were randomized to receive either degarelix 240/160 mg (subsequently 80 mg; $n = 66$) or degarelix 240/80 mg ($n = 69$); 1 patient crossing over from leuprolide to degarelix 240/160 mg did not receive further treatment. Baseline characteristics of patients enrolled in CS21A have been reported previously and were generally comparable between patients who continued on degarelix and those who crossed over from leuprolide to degarelix.⁶ Of the patients enrolled in the extension phase, 65 of 125 (52%) and 81 of 134 (60%) had discontinued from the degarelix group and the leuprolide to degarelix crossover group, respectively (Table 1). Similar proportions of patients in the degarelix and leuprolide groups discontinued because of AEs

Table 1. Patient disposition in CS21A

Group	Degarelix, 240/80 mg, n (%)	Leuprolide → Degarelix, 240/80 or 160 mg, n (%)
ITT CS21A	125 (100)	134 (100)
Completed CS21A	60 (48)	54 (40)
Discontinuations	65 (52)	81 (60)
Adverse event	21 (17)	31 (23)
Lost to follow-up	6 (5)	2 (1)
Protocol violation	1 (<1)	2 (1)
Patient withdrawn by investigator	2 (2)	8 (6)
Patient withdrew consent	7 (6)	7 (5)
Other	28 (22)	31 (23)

ITT, intention to treat.

Table 2. Incidence of treatment-related adverse events ($\geq 5\%$) in patients receiving degarelix or crossing over from leuprolide to degarelix in CS21 and CS21A trials

Adverse Event, n (%)	Degarelix, 240/80 mg	Degarelix, 240/160 mg	Leuprolide → Degarelix, 240/80 or 160 mg	Total
Safety analysis set CS21/CS21A	207 (100)	202 (100)	135 (100)	544 (100)
Any adverse event	132 (64)	129 (64)	85 (63)	346 (64)
Deaths	14 (7)	18 (9)	8 (6)	40 (7)
Injection-site reactions				
Pain	64 (31)	67 (33)	36 (27)	167 (31)
Erythema	40 (19)	50 (25)	26 (19)	116 (21)
Swelling	17 (8)	16 (8)	10 (7)	43 (8)
Nodule	13 (6)	17 (8)	6 (4)	36 (7)
Induration	9 (4)	12 (6)	4 (3)	25 (5)
Hot flush	61 (29)	61 (30)	40 (30)	162 (30)
Weight increased	21 (10)	13 (6)	16 (12)	50 (9)
Pyrexia	13 (6)	15 (7)	9 (7)	37 (7)
Chills	14 (7)	7 (3)	2 (2)	23 (4)
ALT increased	13 (6)	14 (7)	6 (4)	33 (6)
AST increased	11 (5)	10 (5)	5 (4)	26 (5)
Fatigue	6 (3)	13 (6)	8 (6)	27 (5)
Erectile dysfunction	2 (<1)	4 (2)	7 (5)	13 (2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

(17% and 23%, respectively). In total, 163 of 385 patients (42%) completed the extension trial, including 60 patients treated with degarelix 240/80 mg and 54 patients who crossed over from leuprolide to degarelix (240/160 or 240/80 mg).

Primary Objective: Safety and Tolerability

The primary objective of the extension study was to assess the long-term safety and tolerability of treatment with degarelix. The incidence of treatment-related AEs occurring at a frequency of $\geq 5\%$ in any group is summarized in Table 2. Most AEs were of mild or moderate intensity. Overall, the incidence of AEs over 5 years of treatment was similar between patients receiving degarelix 240/80 mg and those who crossed over to degarelix from leuprolide after 1 year of treatment.

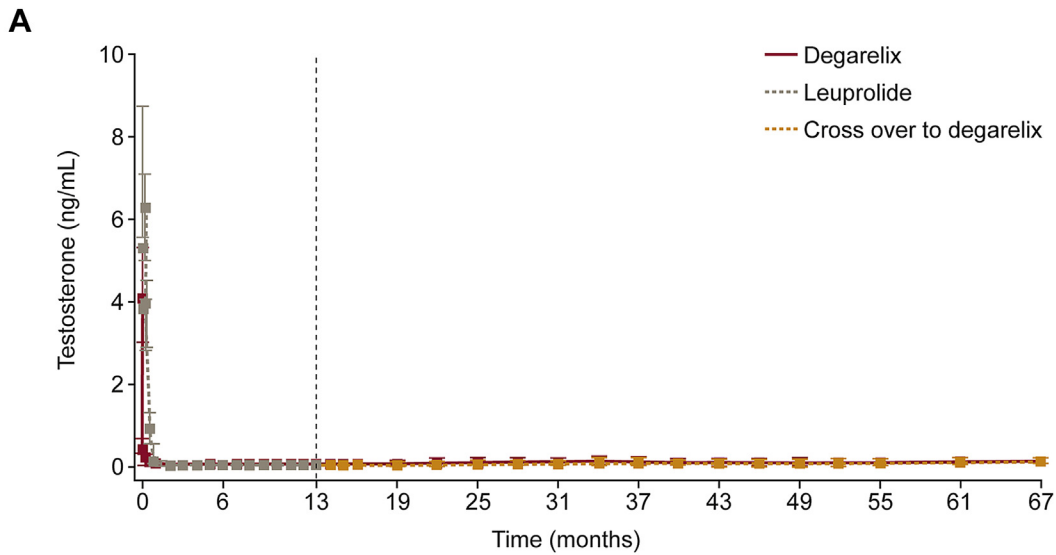
The most common treatment-related AEs experienced by patients enrolled in CS21 and CS21A trials were injection-site reactions. Injection-site reactions included pain, erythema, swelling, and nodules (in 31%, 21%, 8%, and 7% of patients, respectively). Most reactions occurred after the first injection; 31% of 276 degarelix 240-mg initiation doses were reported to be associated with injection-site reactions. Incidence decreased for subsequent

doses, with 2.5% of 9142 maintenance doses of degarelix 80 mg being associated with a reaction. In total, 12 of 544 patients (2%) treated with degarelix during CS21 and CS21A trials discontinued because of injection-site reactions.

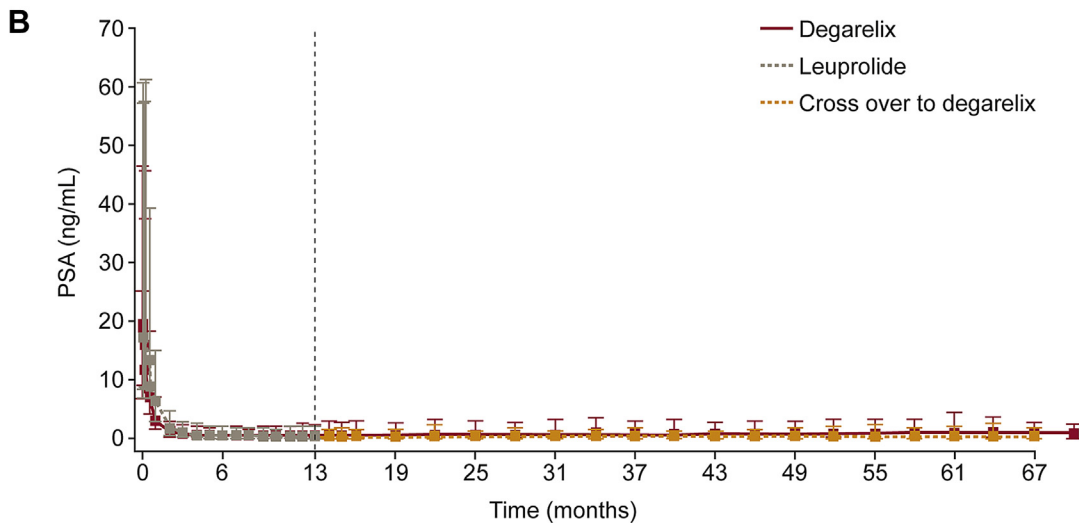
Other AEs related to androgen deprivation included hot flushes and weight gain, which occurred in 30% and 9% of patients, respectively. Pyrexia (7%), chills (4%), and increased alanine aminotransferase or aspartate aminotransferase (6% and 5%, respectively) were also reported. Treatment-emergent serious AEs leading to death were reported for 40 patients (7%); all were considered unrelated or unlikely to be related to trial treatment. The most frequent causes of death were neoplasms (12 patients, including 8 men who died from PCa), cardiac disorders (12 patients), and infections and infestations (5 patients).

Secondary Objectives: Testosterone and PSA Suppression

Long-term suppression (≥ 4 years) of testosterone below castrate levels (median testosterone level ≤ 0.5 ng/mL) was maintained in patients continuing in the study. There was no difference in testosterone levels between the group continuing to receive degarelix and the group



Number of patients												
Degarelix	207	187	167	108	98	89	83	76	70	67	64	40
Leuprolide	200	188	170	113	98	85	77	73	65	61	57	32



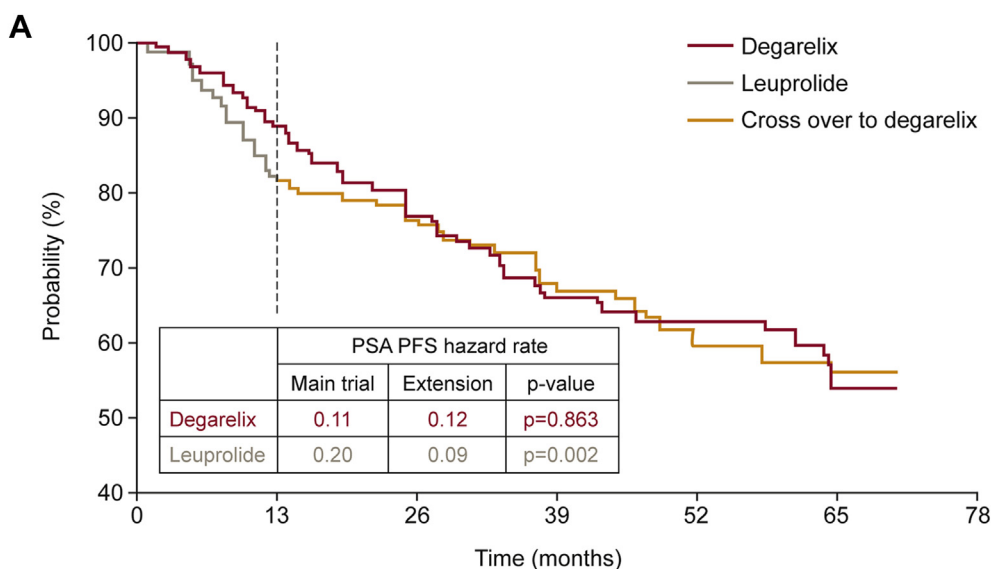
Number of patients												
Degarelix	206	187	168	108	97	89	83	76	69	68	66	40
Leuprolide	200	186	171	113	97	85	77	72	65	62	57	32

Figure 1. Median (interquartile range) absolute testosterone levels (**A**) and median (interquartile range) absolute prostate-specific antigen (PSA) levels (**B**) in the initial 1-year trial and extension phase.

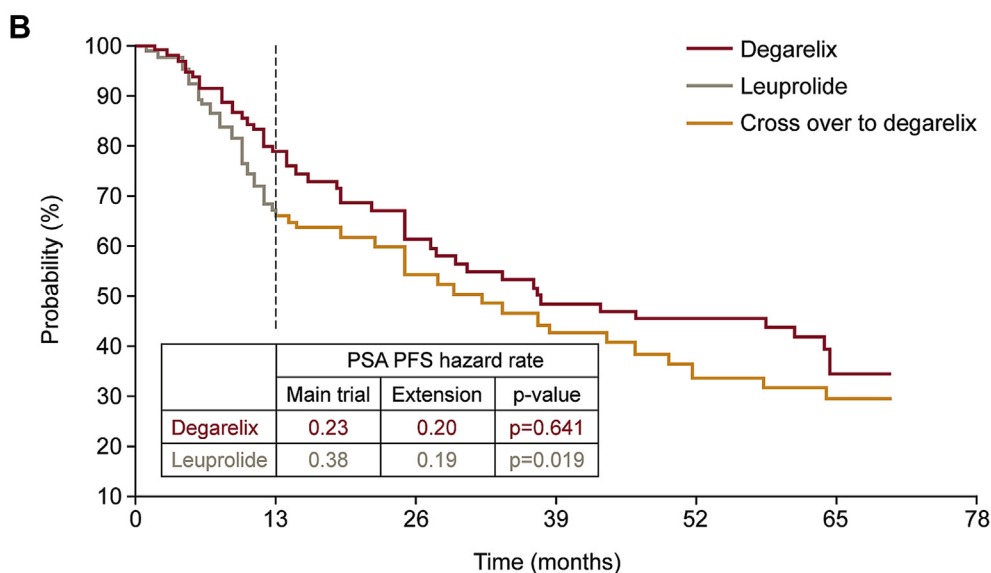
that crossed over from leuprolide to degarelix after 1 year of treatment (Fig. 1A). The primary end point of CS21 and a secondary end point of CS21A was the cumulative probability of testosterone level ≤ 0.5 ng/mL from days 28 to 364 in CS21 and from day 365 to the end of study in CS21A. There was no statistically significant difference in the number of patients escaping testosterone suppression between the treatment groups at any measurement ($P = .548$; log-rank test for homogeneity).

Median PSA levels after 1 year of treatment in CS21 were 0.50 and 0.40 ng/mL in the degarelix 240/80 mg and

leuprolide groups, respectively. Suppression of PSA was maintained in the extension phase: median PSA levels remained < 2 ng/mL for degarelix-treated patients and for those crossing from leuprolide to degarelix (Fig. 1B). The number of patients experiencing PSA failure (defined as a PSA increase of $\geq 50\%$ from nadir and ≥ 5 ng/mL on 2 consecutive occasions at least 2 weeks apart) after 5 years was 46 of 125 (37%) and 49 of 134 (36%) for the degarelix 240/80 mg group and those crossing from leuprolide to degarelix, respectively. There was no statistically significant difference in the number of patients with



Number of patients at risk							
Degarelix	207	152	89	70	60	35	0
Leuprolide	201	144	85	69	55	29	0



Number of patients at risk							
Degarelix	100	72	42	32	27	14	0
Leuprolide	93	56	30	23	17	11	0

Figure 2. Prostate-specific antigen progression–free survival (PSA PFS) probability in all patients (**A**) and those with baseline PSA level ≥ 20 ng/mL (**B**) continuing degarelix 240/80 mg or crossing over from leuprolide to degarelix.

PSA progression between the treatment groups ($P = .665$; log-rank test for homogeneity).

PSA PFS

The risk of PSA PFS decreased in patients who crossed from leuprolide to degarelix during the extension phase (Fig. 2A). The PSA PFS hazard rate for patients crossing from leuprolide to degarelix significantly decreased from 0.20 during the first year to 0.09 during the extension

phase ($P = .002$). For the group continuing on degarelix 240/80 mg, the hazard rate was 0.11 during the first year and 0.12 during the extension ($P = .863$). In patients with baseline PSA levels >20 ng/mL, the PSA PFS hazard rate significantly decreased from 0.38 to 0.19 after crossing from leuprolide to degarelix ($P = .019$; Fig. 2B). The hazard rate for the degarelix 240/80 mg group was 0.23 in the first year and 0.20 in the extension phase ($P = .641$).

COMMENTS

The primary objective of the extension trial was to evaluate safety and tolerability during treatment with the degarelix 1-month dosing regimen for up to 5 years. There was a high rate of discontinuation in both study arms, which was to be expected considering the length of the extension phase, clinical stage, patient age, and monthly injection schedule. Most discontinuations were considered unrelated to study treatment. In total, 42% of patients completed the extension phase, demonstrating good tolerability of the treatment regimen.

During up to 5 years of degarelix treatment, AEs occurred at a similar frequency across the treatment arms. The most frequently reported events were injection-site reactions. The incidence of injection-site reactions occurring when patients crossed from leuprolide to degarelix was similar to that seen in patients initially randomized to degarelix.² In patients crossing to degarelix, the reported injection-site reactions decreased to low levels as the extension trial progressed; most reactions were mild, and discontinuation due to an injection-site reaction occurred in 2% of patients. Injection-site reactions are likely related to the subcutaneous route of administration as skin reactions have also been reported for leuprolide when given subcutaneously.^{8,9}

Chills were reported by 4% of patients. Degarelix is a third-generation antagonist with minimal histamine-releasing activity¹⁰ and no reported incidences of anaphylactic reactions during the clinical development program.^{2,11,12} Other AEs were mainly related to androgen deprivation and the presence of PCa; no new safety signals became apparent during long-term degarelix treatment of up to 5 years.

During CS21, degarelix demonstrated more rapid suppression of LH, FSH, testosterone, and PSA than leuprolide and was as effective as leuprolide in inducing and sustaining testosterone suppression to castrate levels (≤ 0.5 ng/mL).² Degarelix provided long-term suppression (for at least 5 years) of median testosterone levels to below castrate levels. Effective long-term testosterone suppression could be important as ineffective testosterone suppression may be associated with increased PCa mortality,¹³ and breakthrough testosterone levels >0.32 ng/mL have been shown to predict decreased PFS.^{14,15}

PSA progression (or castration-resistant status) often precedes clinically detectable recurrence by years, and effective PSA suppression is associated with improved overall survival.¹⁶⁻¹⁹ In the pivotal CS21 trial, patients receiving degarelix 240/80 mg had a significantly lower risk of PSA progression or death than those receiving leuprolide during the first year of treatment. After crossing over from leuprolide to degarelix, the PSA PFS hazard rate decreased significantly ($P = .002$), indicating a decreased risk of PSA progression or death after switching to degarelix. There was no significant change in the hazard rate for patients who continued to receive degarelix.

Of the patients in CS21A, more than half had advanced disease (locally advanced or metastatic disease). As expected, PSA progression in the first year occurred mostly in patients with locally advanced or metastatic disease and exclusively in patients with baseline PSA level >20 ng/mL.⁴ The risk of PSA progression in patients with baseline PSA level >20 ng/mL was significantly lower for degarelix 240/80 mg vs leuprolide during the first year ($P = .019$). Patients with baseline PSA level >20 ng/mL who crossed over from leuprolide to degarelix experienced a significant improvement in the PSA PFS hazard rate similar to that in the overall population.

Further benefits of degarelix, both clinical and economic, have recently been reported. A pooled analysis of comparative phase III degarelix trials found that the risk of experiencing a cardiovascular event or death is lower for men treated with degarelix compared with a LHRH agonist, particularly in those patients with a history of cardiovascular disease before starting androgen deprivation.²⁰ In economic terms, a recent cost-effectiveness analysis based on data from CS21 demonstrated that degarelix was cost-effective or dominant (better efficacy and lower cost) over leuprolide.²¹ The authors also consider that addition of further differential clinical outcomes between degarelix and leuprolide would likely increase the cost saving and quality-adjusted life years achieved with degarelix treatment.²¹

Limitations are that the study incorporated a 1-way crossover from leuprolide to degarelix, and it did not include a crossover arm from degarelix to leuprolide; thus, there is no direct comparator for the crossover group. The study used a surrogate end point of PSA progression. Because of the length of follow-up, the study does not have sufficient deaths from PCa to draw conclusions about the survival benefit.

CONCLUSIONS

Degarelix 240/80 mg was well tolerated and provided sustained testosterone suppression over a 5-year period. Injection-site reactions were common with the initial dose but uncommon with subsequent doses. Over the 5-year period, degarelix resulted in improved PSA PFS compared with leuprolide.

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