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# Prospective Evaluation of Testosterone Fluctuations During a Transition of Therapy From Degarelix to Leuprolide in Patients on Androgen Deprivation Therapy

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| <b>OBJECTIVE</b>  | To evaluate for a possible testosterone surge during transition of therapy from degarelix to leuprolide.  |
| <b>METHODS</b>    | We conducted an investigator-initiated, prospective, single-arm, open-label trial for evaluation of a potential testosterone surge during a transition of therapy from degarelix to leuprolide. Study patients were administered 3 monthly depot injections of degarelix, followed by one 3-month depot injection of leuprolide. A rise in serum testosterone was considered clinically relevant in previously castrate patients whose testosterone rose above 50 ng/dL.  |
| <b>RESULTS</b>    | Forty-five patients aged 59-86 years were included in the final analysis after completing the entire 6-month study. Nineteen percent of patients had received prior androgen deprivation therapy, and 10% had metastatic disease. Mean serum testosterone was reduced from a baseline of $374.6 \pm 155.7$ ng/dL to $16.5 \pm 8.1$ ng/dL, and prostate-specific antigen reduced from $23.8 \pm 55.8$ ng/mL to $1.6 \pm 3.7$ ng/mL after 3 months of treatment with degarelix. On transition from degarelix to leuprolide (day 90), there was a rise in testosterone from the nadir of 16.5 ng/dL to a peak of 25.8 ng/dL ( $P = .0005$ ), occurring at day 93. Four patients (8.9%) experienced a testosterone surge with a mean peak serum testosterone of 80.7 ng/dL; all 4 returned to castrate levels within 7 days, and all remained asymptomatic throughout the testosterone fluctuation. |
| <b>CONCLUSION</b> | Fluctuations in serum testosterone after this transition of therapy were mild and short-lived with only 8.9% of men experiencing testosterone elevations to noncastrate levels. UROLOGY 83: 670-674, 2014. © 2014 Elsevier Inc.   |

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in adult men in the United States.<sup>1</sup> Androgen deprivation therapy (ADT) remains first-line for the treatment of metastatic prostate cancer and is often used as an adjunct in patients with locally advanced or high-grade disease.<sup>2,3</sup> Long-term medical castration is frequently achieved with a gonadotropin-releasing hormone (GnRH) agonist, such as leuprolide. Given their mechanism of action, leuprolide and other GnRH agonists produce a transient rise in serum testosterone after administration before achieving castration. This luteinizing hormone-driven testosterone “surge” might last up to 3 weeks before resolving.<sup>4-6</sup> Most

patients do not experience symptoms during the surge; however, increases in bone pain, lower urinary tract symptoms, ureteral obstruction, and even cord compression and death have been reported.<sup>7,8</sup> The chance for symptomatic or tumor progression during the testosterone surge, termed a clinical “flare,” has led many clinicians to prescribe a concomitant preventive course of nonsteroidal antiandrogens during ADT induction.

Degarelix is a GnRH receptor antagonist that has been shown to be as effective as leuprolide at inducing and maintaining medical castration.<sup>9</sup> GnRH antagonists produce a rapid reduction in serum testosterone through blockade of the GnRH receptor, resulting in an immediate reduction in luteinizing hormone, follicle-stimulating hormone, and testosterone. Within 3 days of receiving degarelix, 96% of patients can expect to have a castrate level testosterone.<sup>9</sup> Currently, degarelix is only available in a 1-month depot formulation, and patients embarking on long-term ADT often prefer a longer acting medication to reduce the number of office visits and injections required for maintenance. Urologists are then faced with a decision regarding a transition of therapy to a GnRH

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agonist. Additionally, some patients are being started on ADT using an induction regimen with a GnRH antagonist, followed by a transition to a longer-acting GnRH agonist in an effort to circumvent the need for concomitant antiandrogen therapy. In neither of these scenarios have fluctuations in testosterone during the transition from degarelix to a GnRH agonist ever been reported.

## METHODS

We conducted an investigator-initiated, prospective, single-arm, open-label trial for the evaluation of a potential testosterone surge during a transition of therapy from degarelix to leuprolide. Local Institutional Review Board approval was obtained before enrolling patients and gathering data. All patients were counseled on risks associated with the study and signed an Institutional Review Board approved standardized consent form at the time of study entry. Physicians at Urology of Virginia offices recruited all study patients during routine clinic visits.

Patients eligible for study entry included men aged 18 years and older with histologically confirmed adenocarcinoma of the prostate for which ADT was indicated. We excluded men with a baseline testosterone less than 150 ng/dL, an Eastern Cooperative Oncology Group performance score greater than 2, and a history of hormonal manipulation within the past 6 months. Men with metastatic prostate cancer were permitted; however, those with radiographically or pathologically diagnosed brain or spinal metastasis were excluded. Specifically, we excluded patients with metastasis to either the bony vertebral body or leptomeningeal metastasis.

Each patient underwent a screening history, physical examination, and laboratory evaluation including prostate-specific antigen (PSA) and testosterone. Eligible study patients were then administered a starting degarelix dose of 240 mg by two 120 mg deep subcutaneous injections (day 0). This was followed by 2 monthly depot injections of 80 mg each (days 30 and 60). At day 90, patients received a 3-month (22.5 mg) depot injection of leuprolide. All medication was administered at Urology of Virginia offices, and failure to comply with medication timelines resulted in dismissal of the patient from the study. In addition to the screening assessment, serum PSA was measured at days 90 and 180. Serum testosterone was measured at days 0, 30, 90, 91, 93, 97, 104, 111, 118, and 180. Adverse event data were collected at each study visit.

Our primary study end point was the ability to maintain medical castration (ie prevent a testosterone surge) during a transition from degarelix to leuprolide. For the purposes of this study, we considered castrate level testosterone to be any value  $\leq 50$  ng/dL. During the transition, fluctuations in testosterone were considered to be a relevant surge for any previously castrate patient whose testosterone rose above 50 ng/dL. Testosterone elevations were also deemed significant if a patient were to experience a symptomatic exacerbation, such as complaints of increased bone pain. Our secondary end point was assessment of any PSA elevation after the degarelix to leuprolide transition.

Our sample size was selected based on a power analysis for the primary study end point. Using a 2-sided type I error ( $\alpha$ ) level of 0.05 and a power ( $1-\beta$ ) of 0.90, we needed 40 patients to detect a testosterone surge in 4% of the study population. We assumed a dropout rate of 20% which was likely an overestimate given that the patients would be undergoing treatment for prostate cancer, and our study follow-up was short. Therefore, to complete the study with at least 40 patients, our plan for enrollment

**Table 1.** Demographics and prostate cancer history

|  |                       |
|--|-----------------------|
| Age (y)                                | 73 $\pm$ 8 (59-86)    |
| Race, No. (%)                          |                       |
| White                                  | 36 (75)               |
| Black                                  | 11 (23)               |
| Other                                  | 1 (2)                 |
| BMI, kg/m <sup>2</sup> , mean $\pm$ SD | 28.03 $\pm$ 3.82      |
| ECOG performance status                | 0.06 $\pm$ 0.32 (0-2) |
| Total Gleason grade, No. (%)           |                       |
| Score 6                                | 9 (19)                |
| Score 7                                | 17 (35)               |
| Score 8-10                             | 22 (46)               |
| Prior ADT, N (%)                       | 9 (19)                |
| Metastatic prostate cancer, N (%)      | 5 (10)                |

ADT, androgen deprivation therapy; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

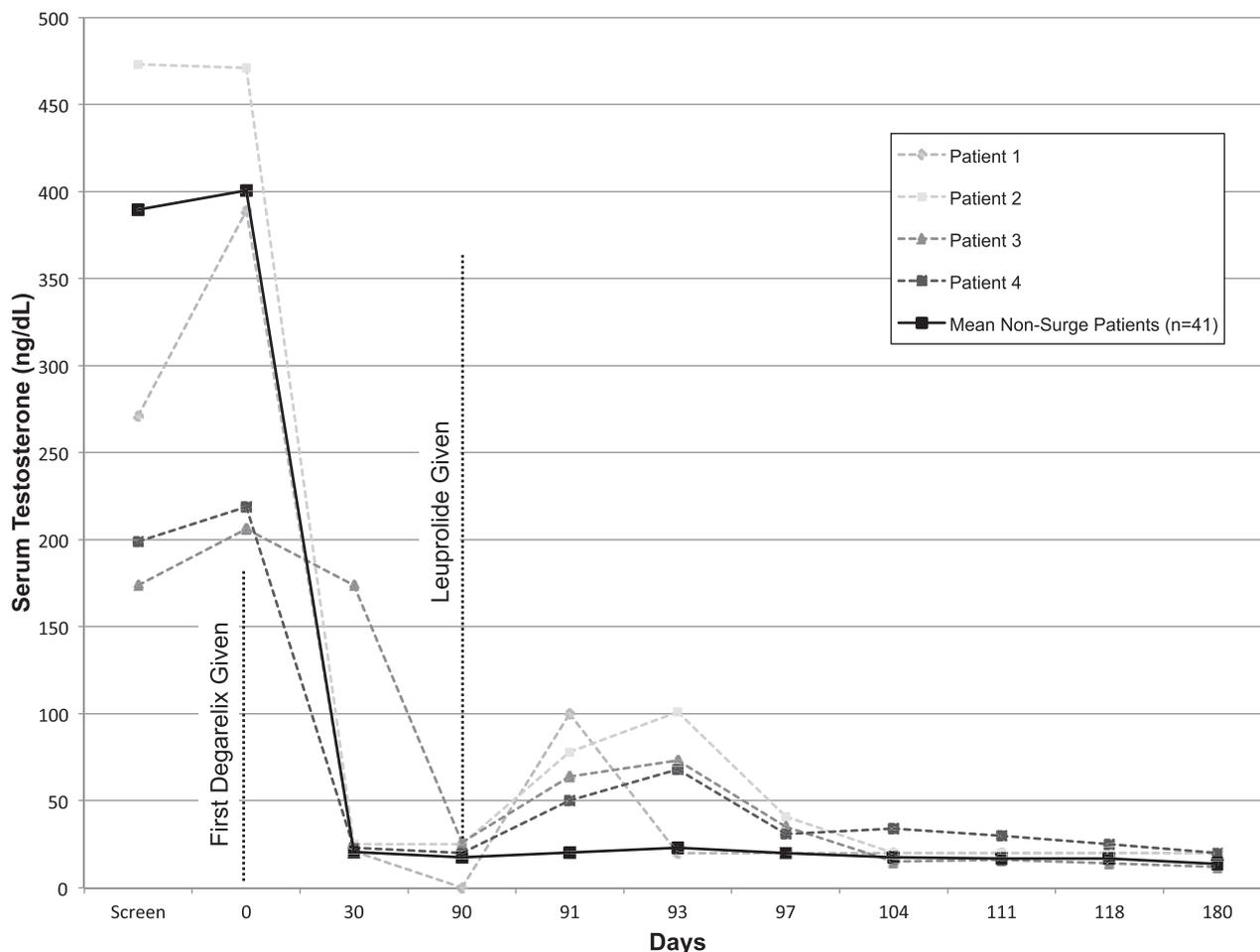
Data are expressed as mean  $\pm$  standard deviation (range) unless otherwise indicated.

was 50 patients. Statistical analysis was performed using SPSS v. 20 software (IBM Corp.). Friedman and Wilcoxon Signed-Rank tests were used for comparisons of testosterone and PSA, respectively. All statistics are reported as mean  $\pm$  standard deviation unless otherwise indicated, and *P*-values of  $<.05$  were considered statistically significant.

## RESULTS

Forty-eight patients aged 59-86 years (mean, 73) were enrolled and completed the entire 6-month study between April 2011 and August 2012. The baseline demographic and prostate cancer history is outlined in Table 1. Nineteen percent of subjects had received prior ADT; however, all had been off hormonal therapy for at least 6 months before study entry and had a baseline testosterone  $>150$  ng/dL. Metastatic disease was present in 10% of patients, and 44% had undergone prior attempted curative treatment.

Three patients (6%) were excluded from analysis because they did not reach castrate level testosterone ( $<50$  ng/dL) before transition to leuprolide. In the remaining cohort of 45 men, mean serum testosterone was reduced from a baseline of  $374.6 \pm 155.7$  ng/dL to  $16.5 \pm 8.1$  ng/dL, and PSA reduced from  $23.8 \pm 55.8$  ng/mL to  $1.6 \pm 3.7$  ng/mL after 3 months of treatment with degarelix. On transition from degarelix to leuprolide (day 90), there was a rise in testosterone from the nadir of 16.5 ng/dL to a peak of 25.8 ng/dL ( $P = .0005$ ), occurring at day 93. PSA continued to decline after leuprolide to  $0.92 \pm 1.7$  ng/mL at completion of the study (compared with PSA at 3 months,  $P = .001$ ). Four patients (8.9%) experienced a testosterone surge with a mean peak serum testosterone on day 91 of 80.7 ng/dL. All 4 patients returned to castrate levels within 7 days after transition; however, their testosterone remained slightly higher than those patients not experiencing a significant surge until day 104 (Fig. 1). From day 97 until completion of the study, all 45 patients remained castrate. No patient experienced a symptomatic flare of his prostate cancer. Notably, the 3 excluded patients who never achieved castration with degarelix induction all experienced a



**Figure 1.** Serum testosterone over time in patients with a testosterone surge compared with mean testosterone of those without a surge.

significant testosterone surge after administration of leuprolide. Their testosterone rose from a mean of 88.7 to 225 ng/dL at day 93, comparable with what we would expect for a hormone-naïve patient given a GnRH agonist alone.

We conducted a univariate analysis and multivariate logistic regression in an effort to predict which patients might be more likely to experience a testosterone surge during the transition to leuprolide. Predictive variables tested include age, race, body mass index, clinical stage, Gleason score, prior ADT, presence of metastatic disease, screening testosterone level, and T level at the time of medication transition. We did not find any significant variables predictive of a testosterone surge on either univariate or multivariate analysis.

Adverse events were minimal and comparable with what has previously been reported with degarelix and leuprolide.<sup>4,9</sup> The primary adverse events were related to ADT itself, such as hot flashes, loss of libido, and fatigue. Ten percent of patients complained of some discomfort at the injection site. No patient required discontinuation of either degarelix or leuprolide, or asked to be removed from the study secondary to an adverse event. There were

no changes or exacerbations in any adverse events during the transition to leuprolide.

## COMMENT

ADT has a long history in the management of prostate cancer. In patients with metastatic disease, ADT constitutes first-line treatment with proven efficacy for androgen dependent tumors and relative tolerability compared with cytotoxic agents.<sup>2</sup> GnRH agonists produce a predictable luteinizing hormone–driven rise in testosterone during the first several weeks of therapy.<sup>6</sup> This surge has been shown to have adverse effects (clinical “flare”) in a portion of patients, especially increased bone pain in patients with bone metastasis. Faure et al<sup>10</sup> first described this phenomenon in 1983. They reported a 10% incidence of bone pain progression during the first week of GnRH therapy. Even more concerning are reports, however scarce, of deaths occurring during GnRH induction presumed secondary to disease flare and possible spinal cord compression.<sup>11,12</sup> Thompson et al<sup>8</sup> reviewed 765 cases in 9 series and found that 10.9% of patients experienced a clinical flare, including 15 who died during the testosterone surge.

The significance of potential disease progression during the testosterone surge prompted the use of short-term antiandrogens. In 1989, Kuhn and Crawford<sup>13,14</sup> separately published prospective, double-blind, randomized controlled trials for ADT induction using a GnRH agonist with or without a concomitant antiandrogen. Kuhn et al<sup>14</sup> randomized a small cohort of 36 patients starting ADT to either buserelin and nilutamide or buserelin and placebo. Using a pain visual analog scale, they demonstrated worsening bone pain in 5 of 17 men in the treatment arm vs 12 of 19 men in the placebo arm ( $P < .05$ ), suggesting antiandrogens block some symptomatic progression during the testosterone surge. Crawford et al<sup>13</sup> randomized over 600 patients to receive androgen deprivation using either leuprolide and placebo or leuprolide and flutamide. Although the primary end point was overall survival, they also evaluated bone pain and found a significant reduction in pain during the first month of therapy in patients receiving antiandrogen compared with placebo. Although effective at ameliorating some flare symptoms, antiandrogens are not a panacea as they are associated with their own side effects, including gastrointestinal and hepatic toxicity, and add additional costs to the patient.

GnRH antagonists act by blocking the GnRH receptor at the pituitary and produce a rapid reduction in testosterone without the surge seen with GnRH agonists.<sup>9</sup> Their mechanism allows them to be used in patients who present with widely metastatic disease and even spinal metastasis without necessitating antiandrogens to block a testosterone surge. However, the monthly dosing required with degarelix can become tiresome to patients in the long-term. To lengthen the dosing interval, these patients might be transitioned to a depot GnRH agonist. Testosterone fluctuations during this transition have not been previously reported.

In 2011, Garnick and Mottet<sup>15</sup> reported on 176 patients receiving ADT induction with abarelix for 12 weeks, followed by maintenance ADT with a GnRH agonist for 8 weeks. They reported that 93.8% of patients were castrate (testosterone  $< 50$  ng/dL) after abarelix induction, and 91% remained castrate through the transition to a GnRH agonist. The mean testosterone in these patients increased from 17.2 to 37.3 ng/dL 6 days after the conversion ( $P$ -value not reported). They did not report any symptomatic progression during the transition despite the small increase in testosterone. Although apparently an effective strategy, abarelix is no longer available in many countries secondary to systemic allergic reactions and hypotension in a significant portion of the treated population.

Here we have reported our data from an investigator-initiated, prospective, open-label study evaluating the effect on testosterone during a transition of therapy from degarelix to leuprolide in patients with localized or metastatic prostate cancer. We found a small but statistically significant increase in mean testosterone from a nadir of

16.5 ng/dL to a peak of 25.8 ng/dL. Four patients (8.9%) achieving castration with degarelix induction experienced a predefined surge during the transition with testosterone levels  $> 50$  ng/dL (Fig. 1). Within 7 days, however, all patients were again castrate and remained so for the duration of the study. This suggests that for patients on long-term ADT who wish to transition from degarelix to a longer-acting GnRH agonist, concomitant antiandrogens during this conversion might be unnecessary. The testosterone fluctuation that we found in this study was mild and transitory; the clinical significance of which is debatable.

We did find that 6% of degarelix-treated patients never achieved a castrate-level testosterone. This is similar to the approximately 3% nonresponder rate reported in the 240/80 mg arm of the degarelix phase 3 trial and underscores the importance of testosterone monitoring to confirm that castrate levels are achieved. Although these 3 patients were excluded from final analysis, it is interesting to note that they all experienced a dramatic testosterone surge with an average 136.3 ng/dL rise from nadir levels. This suggests that nonresponders to GnRH antagonist therapy should be expected to behave similarly to hormone-naïve patients receiving a GnRH agonist. Given these findings, we feel it is critical to ensure a patient has achieved medical castration before any consideration of transition to a GnRH agonist. This is especially true in patients with extensive metastasis and risk for symptomatic progression.

We did not specifically design this study to evaluate a new regimen for ADT induction by a degarelix induction and GnRH agonist maintenance. However, many urologists in the community are already using this strategy in an effort to avoid the use of concomitant antiandrogens despite the lack of objective data regarding the validity with this approach. What we have presented here would suggest that patients achieving castration after GnRH antagonist induction might be transitioned to a GnRH agonist with limited concern for a significant testosterone surge. That being said, we in no way evaluated the potential of using a single 1-month depot of degarelix before the transition of therapy. We therefore would caution against extrapolating these data in support of this abbreviated sequencing for ADT induction.

There are some limitations to this study. Although adequately powered for our primary objective, we did have a relatively small sample, which might limit our analysis. Perhaps with a larger cohort, we would have been better able to discern what factors contribute to a testosterone surge. Our study was limited in its ability to detect symptomatic testosterone flares for 2 reasons. First, only 10% of patients included in this analysis were harboring metastatic disease, which is the only cohort in which we would expect a symptomatic flare. We also did not standardize adverse event reporting, such as pain scores using a visual analog score. Although not our primary study end point, both of these might have limited our ability to detect minor clinical flares.

## CONCLUSION

Serum testosterone remained castrate during a transition of therapy from degarelix to a longer-acting GnRH agonist in greater than 91% of our study population. A testosterone surge was seen in 8.9% of the study patients; however, the elevation was mild and short-lived, suggesting that the use of concomitant antiandrogens is likely unnecessary. That being said, it is essential to measure serum testosterone before any consideration of transitioning patients from degarelix to a GnRH agonist. Noncastrate patients should be expected to have a significant testosterone surge during the transition of therapy and therefore, should receive combined androgen blockade if they are at risk for symptomatic progression.

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## References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10-29.
2. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2007;25:1596-1605.
3. Boccon-Gibod L, Bertaccini A, Bono AV, et al. Management of locally advanced prostate cancer: a European consensus. *Int J Clin Pract*. 2003;57:187-194.
4. Conn PM, Crowley WF Jr. Gonadotropin-releasing hormone and its analogues. *N Engl J Med*. 1991;324:93-103.
5. Weckermann D, Harzmann R. Hormone therapy in prostate cancer: LHRH antagonists versus LHRH analogues. *Eur Urol*. 2004;46:279-283; discussion 283-4.
6. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. The Leuprolide Study Group. *N Engl J Med*. 1984;311:1281-1286.
7. Bubley GJ. Is the flare phenomenon clinically significant? *Urology*. 2001;58(suppl 1):5-9.
8. Thompson IM, Zeidman EJ, Rodriguez FR. Sudden death due to disease flare with luteinizing hormone-releasing hormone agonist therapy for carcinoma of the prostate. *J Urol*. 1990;144:1479-1480.
9. Klotz L, Boccon-Gibod L, Shore ND, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int*. 2008;102:1531-1538.
10. Faure N, Lemay A, Laroche B, et al. Preliminary results on the clinical efficacy and safety of androgen inhibition by an LHRH agonist alone or combined with an antiandrogen in the treatment of prostatic carcinoma. *Prostate*. 1983;4:601-624.
11. Kahan A, Delrieu F, Amor B, et al. Disease flare induced by D-Trp6-LHRH analogue in patients with metastatic prostatic cancer. *Lancet*. 1984;1:971-972.
12. Mahler C. Is disease flare a problem? *Cancer*. 1993;72(suppl 12):3799-3802.
13. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med*. 1989;321:419-424.
14. Kuhn JM, Billebaud T, Navratil H, et al. Prevention of the transient adverse effects of a gonadotropin-releasing hormone analogue (buserelin) in metastatic prostatic carcinoma by administration of an antiandrogen (nilutamide). *N Engl J Med*. 1989;321:413-418.
15. Gammick MB, Mottet N. New treatment paradigm for prostate cancer: abarelix initiation therapy for immediate testosterone suppression followed by a luteinizing hormone-releasing hormone agonist. *BJU Int*. 2012;110:499-504.