



Brief Report

Avoiding Too Early Repeat Dosing of Depot Leuprolide 6-Month Formulation Using Serial Serum Testosterone and PSA Monitoring

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Abstract

Intramuscular depot leuprolide produces reversible medical castration in men with prostate cancer. Although it is presumed that its hormonal effect wears off at the end of the labelled dosing interval, persistent suppression after a dose has been documented. Patient factors associated with a longer duration of castration include patient age greater than 70 years old, history of radiation therapy to the pelvic region, serum testosterone levels below the normal range prior to the start of leuprolide, and leuprolide treatment duration of one year or more. Based on a 2025 pharmacokinetic simulation modeling study in 1000 virtual subjects, the authors suggested that the next dose of leuprolide 6-month formulation could be delayed for three additional months [1]. The results of this simulation are supported by prospective clinical studies, which are summarized here. However, the duration of response to depot leuprolide is variable based on patient factors. Thus, we recommend performing assessments on each patient to determine the optimal dosing interval. To do so: (1) Obtain pre-treatment serum testosterone and Prostate Specific Antigen (PSA). (2) Establish the PSA nadir by repeating PSA three and six months after the first dose of leuprolide and every three months after the second dose. (3) Document that leuprolide produces and maintains medical castration. (4) Repeat leuprolide dose when the serum testosterone level is above 20 ng/dL. (5) If serum testosterone is at castration levels but repeat PSA levels increase above the nadir, evaluate the patient for castration-resistant prostate cancer, which should be treated accordingly.

Keywords: Dosing interval; Leuprolide; LHRH agonist; Prostate cancer

Introduction

Recently, a computer simulation model showed that an intramuscular depot leuprolide 6-month formulation suppressed serum testosterone levels to 20 ng/dL (0.7 nmol/L) or 50 ng/dL (1.7 nmol/L) in 90% of patients for an effective duration of 10.2 or 12.0 months, respectively [1]. This corroborates clinical reports of persistent suppression of serum testosterone levels

long after a dose of depot leuprolide was administered. Persistent androgen suppression appears to be associated with several patient factors. A summary of relevant studies is reported here. We apply the pharmacokinetic simulation data on depot leuprolide's effective duration to the 2026 American Urological Association Guideline on Advanced Prostate Cancer [2] and provide clinical recommendations on using serial levels of serum testosterone and Prostate Specific Antigen (PSA) to determine the timing of the next dose of depot leuprolide 6-month formulation.

Leuprolide, a Luteinizing Hormone Releasing Hormone Agonist (LHRH-A), is a commonly used method of androgen deprivation therapy for prostate cancer management. It suppresses Leydig cell production of testosterone. The target serum testosterone level in treated patients is 20 ng/dL (this is desired serum testosterone for castration in Europe) or 50 ng/dL (this is the target serum testosterone in the leuprolide package insert in the United States) [3]. It is commercially available as an intramuscular depot formulation that lasts 1, 2, 4, or 6 months, depending on the dose administered. Package labelling advises that a repeat dose should be given when the previous dose wears off.

Published Studies of the Time to Recover Normalization of Serum Testosterone Levels After Discontinuation of Leuprolide

Although there are many published studies of the time it takes to achieve total serum testosterone levels in the normal range after discontinuation of a LHRH-A, some are limited because serum testosterone levels were not collected at regular intervals after stopping the LHRH-A in the majority of patients [4,5], the dose and duration of LHRH-A were not clearly described [6-8], follow-up was too short for serum testosterone testing to determine when serum levels returned to the normal range, or the timing of the increase of serum testosterone levels to above castration levels was not well described [7]. However, some early reports observed that a single dose of an LHRH-A produced persistent hypogonadal symptoms long after the expected duration of the depot formulation, and this finding stimulated further formalized study on this topic [6,8,9].

Table 1 includes prospective studies with more complete data about the leuprolide dosing regimen and duration, and when serum testosterone levels increased to above castration levels. Table 1 excludes three studies that included Japanese patients only [6,10,11]. These patients received 50% of the usual dose of leuprolide (i.e., 3.75 mg monthly) used in the United States. Therefore, the applicability of the study results to non-Asian populations is limited.

An analysis of the studies included in Table 1 shows that:

- Although repeat doses of depot leuprolide are labelled to be given at specific intervals of 1,3,4, or 6 months, the duration of a depot leuprolide dose is variable. That is, in some patients, a single dose of LHRH-A, which is labelled as a 3-month formulation, may suppress testosterone levels for a much longer duration than three months [12-15].
- A continuous leuprolide treatment course greater than one year appears to cause greater suppression of Leydig cells than shorter courses. Return of serum testosterone levels to the normal range may take six to nine months after the last dose of leuprolide [13,14].
- Patient factors that have been associated with slow recovery of Leydig cell function from LHRH-A treatment include patient age greater than 70 years old [13,14] and those with low serum testosterone levels at baseline [15].

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Reference	Number of Patients with Prostate Cancer	Patient Characteristics	Leuprolide Dosing Regimen	Time to Achieve Castration Levels of Serum Testosterone After Administration of Leuprolide Dose	Time to Achieve Serum Testosterone Above Castration Level after Leuprolide or LHRH-A was stopped	Time to Return to Baseline Serum Testosterone after Leuprolide or LHRH-A was stopped
Oelefein, et al, 1998 [12]	13	<p>Median patient age: 65 years old (range, 61-76 years old)</p> <p>Baseline serum testosterone 400 ng/dl (normal, 241-827 ng/dL)</p> <p>Number of patients with radiation therapy: 6</p>	<p>12 patients received leuprolide 22.5 mg as a single dose.¹</p> <p>1 patient received goserelin 10.8 mg as a single dose.¹</p> <p>LHRH-A's were administered as neoadjuvant before prostatectomy or radiation therapy.</p>	<p>Castration level of testosterone was 20 ng/dL or less; or 5% of pretreatment lab value.</p> <p>Three and six months after single dose, serum testosterone was 10 and 20 ng/dL, respectively.</p>	<p>Median time: 7 months after dose of depot leuprolide.</p> <p>Radiation therapy did not affect castration duration after LHRH-A dose.</p>	<p>Median time: 18 months</p> <p>Median duration of hypogonadal symptoms (hot flashes and sweats) was 13.6 months.</p> <p>No patient achieved a return to pre-treatment serum total testosterone levels 18 months after leuprolide dose.</p>

Nejat, et al, 2000 [13]	68	<p>Median patient age: 71 years old (29 patients were younger than 70 years old; range 46-88 years old)</p> <p>Baseline serum testosterone: not measured</p> <p>Number of patients with radiation therapy: 51</p>	<p>35 patients received goserelin 3.6 mg monthly or 10.8 mg every 3 months.</p> <p>30 patients received leuprolide 7.5 mg monthly or 22.5 mg every 3 months.</p> <p>3 patients were switched between the 2 LHRH-As. Patients received one- or three- month formulations</p> <p>Median duration was 9 months (range 3-122 months).</p> <p>LHRH-A was given as a neoadjuvant to radiation therapy (51 patients) or for advanced prostate cancer (17 patients).</p>	Not reported	Not reported	<p>Serum testosterone normal range was 270-1070 ng/dL.</p> <p>After stopping LHRH-A, median time to normalization of serum total testosterone was 7 months (range 1-58 months).</p> <p>At 3, 6, and 12 months after discontinuation of the LHRH-A, 28%, 48%, and 74% of men achieved normal serum total testosterone levels, respectively.</p> <p>Authors concluded that majority of patients had normalization of serum testosterone one year after the last LHRH-A dose.</p> <p>Serum testosterone took longer (22 months) to return to normal in patients on LHRH-A for 24 months or longer as opposed to patients who received courses less than 24 months. In the latter group, serum testosterone normalized in 6 months.</p> <p>41% of patients were younger than 70 years old and 59% of patients were older than 70 years of age. Younger patients achieved normal serum testosterone levels at 6 months, whereas older patients did so in 9 months.</p>
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Kobayashi, et al, 2006 [14]	10	Mean patient age: 76 years old (range, 63-85 years)	Goserelin 3.6 mg (5 patients) monthly	Castration level of serum testosterone was 50 ng/dL or less in 8 patients and 20 ng/dL in 2 patients.	Testosterone normal range was 270-1070 ng/dL.	Not reported
		Baseline serum testosterone not done	Leuprolide 3.75 mg (5 patients) monthly	Not reported. Patients selected for this study had been using an LHRH-A for 30 months or more, had no symptoms or signs of prostate cancer progression, and had a stable PSA less than 1.0 ng/ml. After patients consented for this study, LHRH-A was discontinued.	All patients had serum total testosterone levels above 50 ng/dL within 26 to 327 days (median 98 days) after LHRH-A was stopped.	
			LHRH-A duration 30-56 months.		Patients whose serum testosterone recovered within 100 days after LHRH discontinuation were younger and had shorter courses of LHRH-A.	

Gulley, et al, 2005 [15]	80	Median patient age: 66 years (range, 49-86 years old)	2 doses of 3-month formulation of leuprolide 22.5 mg or goserelin 10.8 mg used as neoadjuvant, adjuvant, or intermittent androgen deprivation therapy after radiation, radical prostatectomy, or both for localized prostate cancer.	Castration level of serum testosterone was 50 ng/dL or less.	Median time: 12.9 weeks with more than 90% of patients achieving this in 18 weeks after the last dose of LHRH-A.	Normal range of serum testosterone was 212-742 ng/dL.
		29 patients had prior radiotherapy alone		Not reported. Patients selected for this study had been using LHRH-A for six months, and then LHRH-A was discontinued.	10% of patients took up to 40 weeks after the last dose of LHRH-A.	Median time: 16.6 weeks after the last dose of LHRH-A. More than 80% of patients achieved this in 24 weeks after the last dose of LHRH-A.
		29 patients had both radical prostatectomy and radiotherapy prior to LHRH-A			It took 12.2 weeks for serum testosterone to increase to 50 ng/dL or higher in 5 patients with low baseline serum testosterone levels less than 212 ng/dL.	For the 5 patients with low baseline serum testosterone levels less than 212 ng/dL, none of them had a return to the normal range of serum testosterone after a median of 27.4 weeks (range, 9-66.7 weeks).
		Baseline serum testosterone levels before GnRH agonist treatment were available in 61 patients. In this subgroup, 56 patients had baseline serum testosterone levels of 212 ng/dL, and 5 patients had baseline serum testosterone levels of 50-211 ng/dL				

¹Depot leuprolide 22.5 mg and goserelin 10.8 mg are labelled as 3- month formulations.

Table 1: Prospective Clinical Studies of Time to Achieve Castration Levels of Serum Testosterone with Depot Leuprolide and Time for Serum Testosterone to Return to Pretreatment Level After Depot Leuprolide Was Stopped.

Discussion

Clinical Implications of the Delayed Recovery of the Hypothalamic Pituitary Gonadal Axis After Discontinuation of Leuprolide

- The delay in recovery of serum testosterone levels to the normal range is because of leuprolide's effect on Leydig cells. Testicular biopsies of leuprolide-treated patients show a decrease in number, involution, and inactivity of Leydig cells [3,16,17].
- Delayed recovery of Leydig cells is associated with increased patient age above 70 years, long courses of LHRH-A greater than one year, and low serum testosterone levels prior to LHRH-A treatment. Previous radiation therapy to the pelvis has also been implicated [18]. Therefore, the duration of delayed recovery is variable based on patient factors.
- Prior to the start of leuprolide, serum testosterone and PSA should be obtained to establish the patient's baseline for both labs.
- After the first dose of 6-month depot leuprolide is administered, serial serum testosterone and PSA testing should be done every three months to document if castration has been achieved and to establish the PSA nadir. These post-dosing labs should be used as the basis of comparison for subsequent labs done during the treatment course. If PSA continues to decrease after the first dose, repeat lab testing every three months after the second dose of depot leuprolide is needed to identify the PSA nadir [2,19,20].
- A dose of 6-month depot leuprolide can be expensive (several hundred dollars or more, depending on a patient's health insurance coverage). For patients concerned about the out-of-pocket costs of treatment for prostate cancer, measuring serial serum testosterone levels after the end of the dosing interval is recommended. If serum testosterone is 20 ng/dL or less, it is reasonable to delay the next dose [3,12,19,20]. Such practice avoids unnecessary and too early administration of follow-up doses of depot leuprolide [12, 19,20].
- PSA secretion is stimulated by testosterone. Once leuprolide produces medical castration, PSA should decrease. Therefore, a PSA increase in the presence of effective medical castration is a harbinger of the development of androgen-insensitive prostate cancer [2]. It is recommended that serial PSA monitoring every three to six months be routinely employed in all patients with prostate cancer; particularly in patients who receive leuprolide for two or more years, when androgen-independent prostate cancer is most likely to develop.

Conclusion

For patients who require continuous 6-month depot leuprolide therapy, repeat dosing can be delayed if the previous dose continues to suppress serum testosterone to castration levels and serial PSA levels are maintained at the nadir.

Return of serum testosterone levels to above castration levels may be delayed for months after a dose of depot leuprolide 6-month formulation. Thus, consistent with the American Urological Association Guideline on Advanced Prostate Cancer [2], prescribers should: (1) establish baseline serum testosterone levels and PSA prior to the start of leuprolide; (2) administer the first dose of depot leuprolide 6-month formulation, then obtain serum testosterone every three months until medical castration has been achieved and obtain PSA levels every three months to identify the PSA nadir, (3) if serum testosterone level has not decreased to the desired castration level of 20 ng/dL or 50 ng/dL, administer the second dose of leuprolide six months after the first dose and obtain serum testosterone and PSA levels every 3 months until serum testosterone achieves the desired medical castration and a PSA nadir level is achieved; (4) delay the next dose of leuprolide until the serum testosterone increases above the desired castration level; (5) if serum testosterone is at castration levels, but repeat PSA levels increase above the nadir, evaluate the patient for castration-resistant prostate cancer, which should be treated accordingly.

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