Effectiveness of Subcutaneously Administered Leuprolide Acetate to Achieve Low Nadir Testosterone in Prostate Cancer Patients

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Evidence suggests lower nadir testosterone levels during the first year of androgen deprivation therapy improve advanced prostate cancer clinical outcomes. We evaluated pivotal trials for subcutaneously administered leuprolide acetate (1-, 3-, 4-, and 6-month doses) to determine nadir testosterone levels. Pooled analysis showed 99%, 97%, and 91% of patients reached nadir testosterone ≤20, ≤10, and ≤5 ng/dL respectively (median ≤3 ng/dL). Across all available categories, ≥88% of patients reached nadir testosterone ≤5 ng/dL, and <3% experienced a microsurge. Achievement and maintenance of low nadir testosterone levels may improve progression-free survival and time to onset of castrate-resistant prostate cancer.

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KEY WORDS

Prostate cancer • Leuprolide acetate • Nadir testosterone • Androgen deprivation therapy • LHRH agonist

Prostate cancer (PCa) is the second most common cancer afflicting men in the United States, with approximately 13% of men receiving this diagnosis during their lifetime.[1] PCa is an androgen-dependent neoplasm and proliferates in the presence of testosterone (T).[2] Suppression of T can inhibit the growth of cancer and is the underlying concept for androgen deprivation therapy (ADT) based on the original research conducted by Huggins and Hodges in 1941.[3] Luteinizing hormone-releasing hormone (LHRH) agonists such as leuprolide acetate (LA) are the most commonly used drugs for ADT with the

objective of reducing T to castrate levels.

In the United States, the biochemical and regulatory definition of castration is T <50 ng/dL, based on the sensitivity of the assays available when ADT was first developed 50 years ago.[2,4] With the advent of improved assays, T now can be measured to much lower limits of quantification (LOQ) of <3 ng/dL.[5] T levels of 20 to 32 ng/dL during ADT are associated with a delay in onset of castrate-resistant PCa (CRPC) and lower risk of death for patients compared with those with higher T levels,[2,6] suggesting the lowest possible serum T should be the objective of ADT. Consequently, in the 2012 Bethesda consensus published by a group of US experts, a 20 ng/dL threshold for serum T during ADT in patients with advanced PCa was recommended, although American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) guidelines have not adopted this recommendation.[7] In 2014, the European Association of Urology (EAU) updated its guidelines for the treatment of PCa to redefine target level of T during ADT to <20 ng/dL.[8]

Nadir serum T, the lowest value during ADT, has been associated with delay in disease progression and improved survival.[9,10] However, although data on nadir T levels have been reported with some therapies (ie, abiraterone acetate with ADT),[11-13] no data have been published on nadir T levels achieved with LHRH agonist monotherapy.

To address this gap in knowledge, a secondary evaluation was conducted by pooling patients from four pivotal trials of LA injected subcutaneously (SC) (SC-LA; ELIGARD®, leuprolide acetate for injectable suspension; Tolmar Pharmaceuticals, Inc., Fort Collins, CO). The LA formulations are composed of a unique, biodegradable, dual polymer-based, extended-release delivery system. SC-LA is available in 1-, 3-, 4-, and 6-month doses that form solid implants upon interaction with SC fluid and subsequently slowly release LA.[14,15] SC-LA maintains mean serum LA levels between 0.1 and 1.0 ng/mL and produces consistent T suppression to ≤20 ng/dL.[16,17]

Materials and Methods

Study Design

Data were pooled from four prospective, open-label, fixed-dose clinical trials in patients with advanced PCa.[14-17] Briefly, patients aged 40 to 86 years with PCa and no prior use of ADT received one of four formulations of SC-LA: (1) 7.5 mg every 28 days for 24 weeks (1-month formulation; n = 120); (2) 22.5 mg every 84 days for 24 weeks (3-month formulation; n = 117); (3) 30 mg every 112 days for 32 weeks (4-month formulation; n = 90); and (4) 45 mg every 168 days for 48 weeks (6-month formulation; n = 111) in accordance with the manufacturer's instructions. The primary endpoint was serum T and secondary endpoints included serum LH, bone pain, urinary symptoms, and World Health Organization (WHO) performance status. Serum T concentrations were measured at screening, baseline, 2, 4, and 8 hours after dosing, days 1, 2, 3, and 7, and then every week until the next dose, following which the sampling schedule was repeated until the end of each study.

Assessments

Serum T was measured by radioimmunoassay with an LOQ of 3 ng/dL; values below this level were recorded as ≤3 ng/dL. Nadir T was defined as the lowest value observed during treatment. Serum T and nadir T concentrations were summarized using descriptive statistics. Microsurges were identified as absolute increases in T of >25 ng/dL within 4 weeks after administration of a second dose. The onset of T suppression and the proportion of time serum T remained below 50 ng/dL, 20 ng/dL, and 10 ng/dL levels were calculated by extrapolating the point at which the T level first crossed the target, calculating the total time T levels remained below the target, and then dividing this by the total time after the target was first achieved (Figure 1).

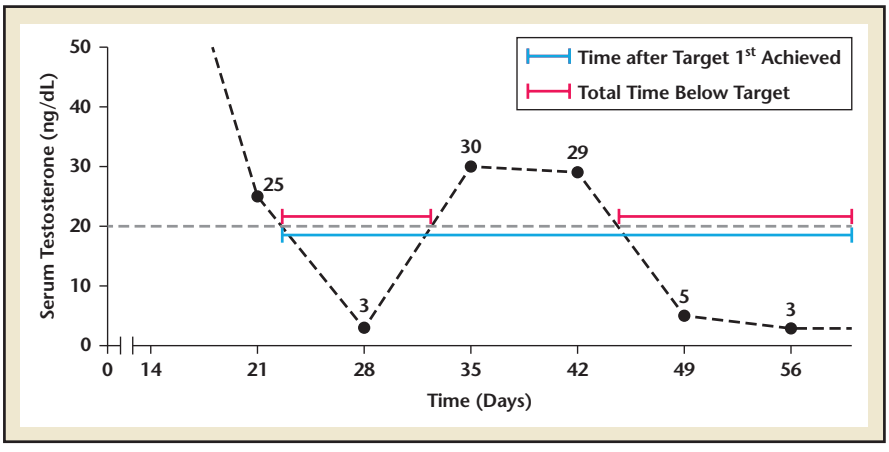

Figure 1. Proportion of time testosterone below suppression target* (illustrative for T ≤20 ng/dL). *Proportion of time below target calculated by dividing the total time below target by the time after target first achieved.

Results

Patient Demographics and Baseline Characteristics

There were 120, 117, 90, and 111 patients in the 1-, 3-, 4-, and 6-month trials, respectively. Baseline characteristics and demographics were similar between study cohorts and mean baseline serum T concentrations ranged from 361 to 386 ng/dL (Table 1).

Onset and Maintenance of Testosterone Suppression

In the pooled population, median onsets of T ≤50, ≤20, and ≤10 ng/dL were 21, 28, and 35 days, respectively (Figure 2A). These durations were the same in each trial, except for the 1-month formulation where the median onset of T ≤10 ng/dL was 7 days earlier at 28 days. The mean proportions of time T suppression was maintained below each target were 100% for T ≤50 ng/dL, 94% to 99% for T ≤20 ng/dL, and 66% to 85% for T ≤10 ng/dL (Figure 2B).

Nadir Testosterone

Pooled analysis showed 99%, 97%, and 91% of patients reached nadir T ≤20 ng/dL, ≤10 ng/dL, and ≤5 ng/dL, respectively, with 80% achieving a nadir T below the LOQ of 3 ng/dL (Figure 3). When comparing each formulation, 93%, 88%, 90%, and 93% of patients who received the 1-, 3-, 4-, and 6-month doses, respectively, reached a nadir T ≤5 ng/dL.

Testosterone Microsurges

Microsurge in T occurred in 0.9% to 3.4% (pooled 1.9%) of patients across the four studies after the second dose (Table 2). Of the eight patients who experienced microsurge, six maintained T below 50 ng/dL and two patients exceeded it.

TABLE 1

Patient Demographics and Baseline Characteristics

	SC-LA Formulated With a Biodegradable, Dual Polymer-based, Extended-release Delivery System Dose Groups			
	1 Month, 7.5 mg (n=120)	3 Month, 22.5 mg (n=117)	4 Month, 30 mg (n=90)	6 Month, 45 mg (n=111)
Mean age (range)	72.8 (52-85)	73.1 (46-85)	73.5 (53-84)	73.2 (50-86)
Age, years, n (%)				
40-49	0	1 (0.9)	0	0
50-59	8 (6.7)	6 (5.1)	6 (6.7)	6 (5.4)
60-69	28 (23.3)	27 (23.1)	20 (22.2)	25 (22.5)
70-79	60 (50.0)	52 (44.4)	42 (46.7)	55 (49.6)
80-89	24 (20.0)	31 (26.5)	22 (24.4)	25 (22.5)
Height, in, mean (range)	69.0 (62-75)	68.2 (55-74)	69.0 (60-78)	68.9 (62-76)
Weight, lbs, mean (range)	185.3 (126-287)	186.1 (130-296)	196.5 (133-313)	190.1 (109-321)
Race, n (%)				
White	92 (76.7)	93 (79.5)	71 (78.9)	84 (75.7)
Black	15 (12.5)	13 (11.1)	10 (11.1)	19 (17.1)
Hispanic	13 (10.8)	7 (6.0)	8 (8.9)	6 (5.4)
Asian	0	3 (2.6)	0	1 (0.9)
Other	0	1 (0.9)	1 (1.1)	1 (0.9)

SC-LA, subcutaneously administered leuprolide acetate.

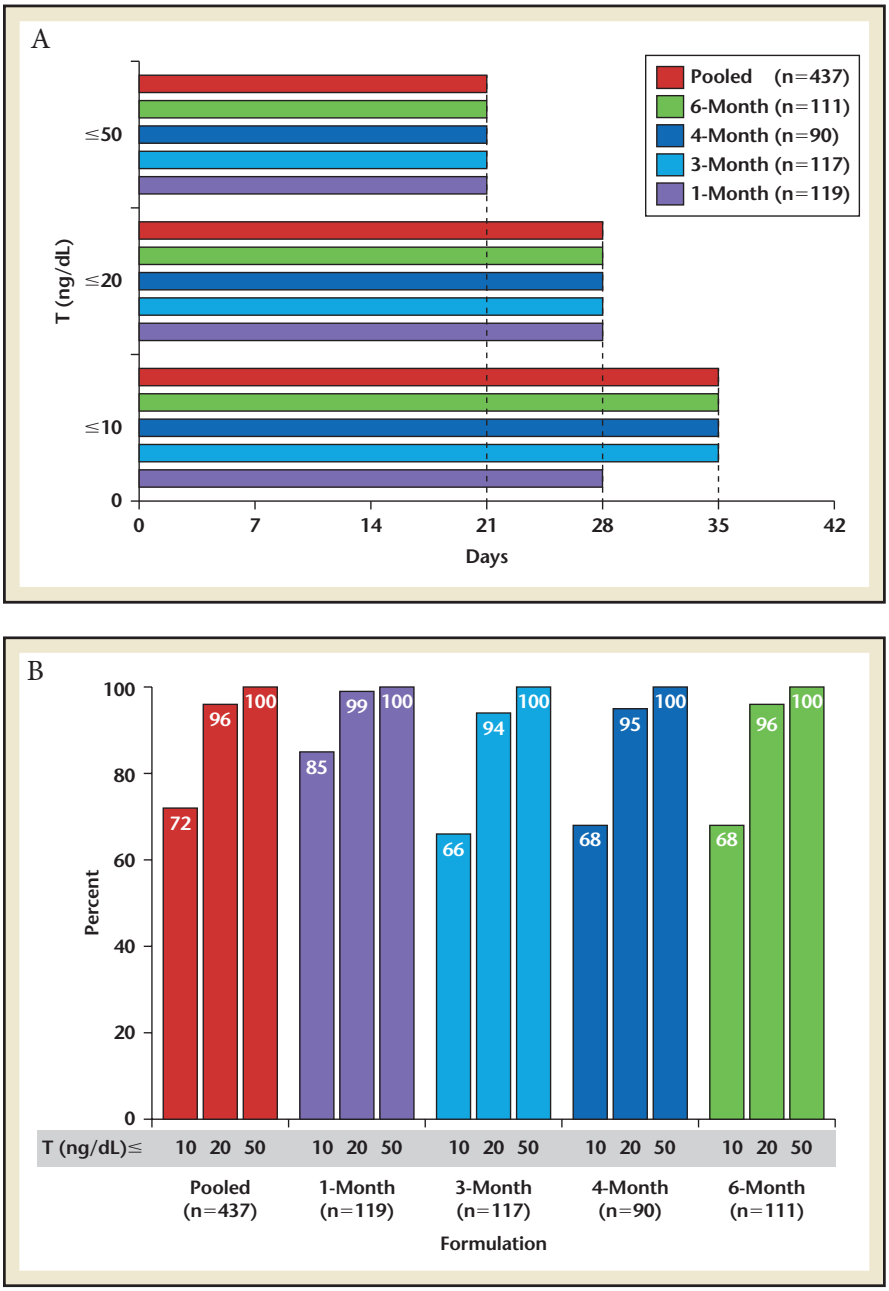

Figure 2. **(A)** Median time to testosterone ≤10, ≤20, or ≤50 ng/dL. **(B)** Proportion of time testosterone levels maintained ≤10, ≤20, or ≤50 ng/dL.

Safety

The safety profiles in the pivotal trials have been previously described and, as expected, were consistent with known effects of LHRH agonist therapy.[14–17]

Discussion

Treatment of advanced PCa patients with SC-LA resulted in reliable T suppression to ≤50 ng/dL by 3 weeks, ≤20 ng/dL by 4 weeks, and ≤10 ng/dL by 5 weeks. Nadir T levels were below the LOQ of 3 ng/dL in 80% and ≤5 ng/dL in 91% of the pooled patient population. SC-LA maintained consistently low T levels, with 100%, 94% to 99%, and 66% to 85% of the treatment durations having T levels below 50, 20, and 10 ng/dL, respectively, across the four formulations. The incidence of microsurge was 1.9%, which is lower than reported for intramuscular-LA (4%) in a phase 3 study.[18,19] SC-LA produced profound T suppression to levels below historic targets and those achieved by surgical castration. This T suppression profile may extend time to disease progression and improve patient survival.[9] In some patients, SC-LA suppresses T to the very low levels reported with the new androgen pathway inhibitor drugs for treatment of advanced PCa, such as abiraterone acetate (alone or combined with ADT).[20,21] Abiraterone (a CYP17A1 inhibitor) with ADT suppresses T levels to near zero.[22] Enzalutamide and apalutamide, also with ADT, impact the androgen signaling pathway by blocking the activity of androgens at the AR within the cells.[23] With the recent approvals of abiraterone in metastatic castrate-sensitive PCa and apalutamide in non-metastatic CRPC, androgen pathway inhibitors now have indications across a wider spectrum of disease, drive overall T signaling to near zero, and improve survival and other endpoints.[11,12,22,23] The publications of studies for these drugs do not disclose the magnitude of T reductions achieved in patients who were randomized to the control arms that received ADT alone. These data would be informative and might identify differences in T suppression between various forms of ADT and their impact on clinical endpoints.

Achieving very low nadir T levels during the first year of ADT may be prognostic for improved cancer-specific survival.[9] It would be informative to understand how effective ADT drugs are in achieving these very low levels by consistently measuring T throughout treatment. The results of our analyses confirm the efficacy of SC-LA in achieving and maintaining T levels below 20 ng/dL, and reaching nadir T

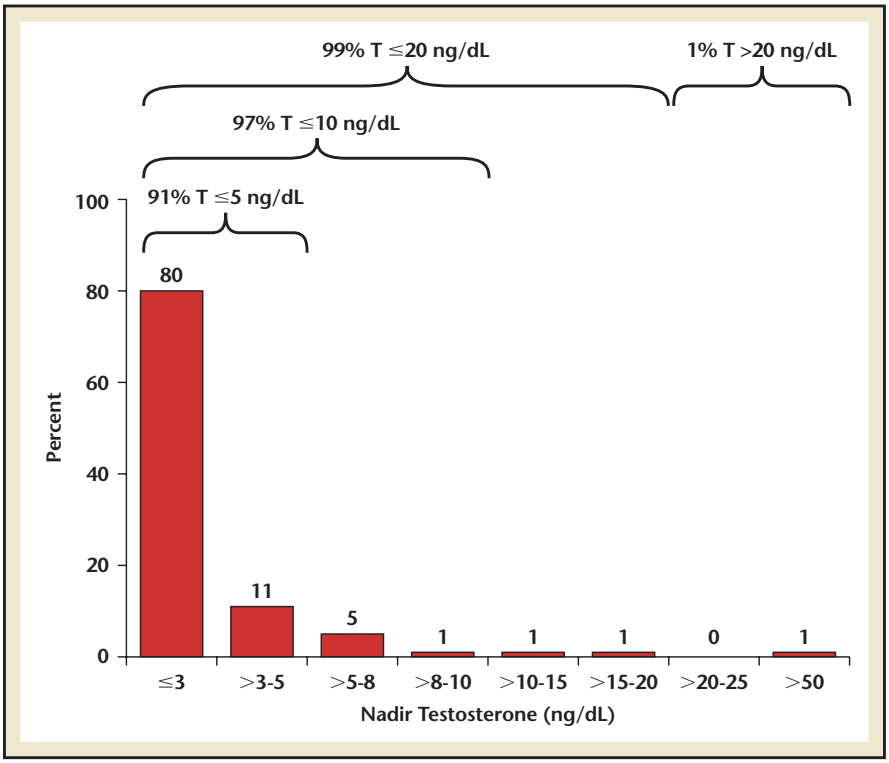

Figure 3. Proportion of patients by nadir testosterone level achieved over study duration (n = 437).

≤3 ng/dL in 80% of patients, providing confidence that patients receiving SC-LA can achieve and maintain very low T levels.

Potential limitations of these analyses are the assessment of nadir T was not a primary objective of the studies and there may be analytical issues associated with pooling of data from multiple studies. However, these are mitigated as the studies had almost identical designs and objectives, including consistent assessment of T levels and use of a single, central laboratory for the assays.

In conclusion, SC-LA provides consistent, stable, and durable T suppression to levels far below those previously defined as adequate for medical castration in PCa patients. With the increasing understanding of the relevance of nadir T levels during ADT, greater consideration should be given to the drug and formulation selected for initiating ADT based on the available data on T suppression. Future studies should assess if there are clinical benefits of achieving very low nadir T levels and compare T suppression levels between various drugs and formulations. ■

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CMP has held consulting or advisory roles for Tolmar, Janssen, Medivation, Bayer, and Dendreon. PT has held a consulting or advisory role for Tolmar. JR has held consulting or advisory roles for Tolmar, Ferring, Bayer, Astellas, Sanofi, Janssen, and GenomeDx. JH has held a consulting or advisory role for Tolmar. DMB and SA are employees of Tolmar Pharmaceuticals, Inc. SE has held consulting or advisory roles for Tolmar, Janssen, and Medivation.

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TABLE 2

Incidence of Microsurges Within 4 Weeks After Second Dose

Formulation[a]	Number of Patients Experiencing Microsurge With Peak	
	≤50 ng/dL	>50 ng/dL
1 month (n=113)	1	0
3 month (n=115)	2	0
4 month (n=88)	1	2
6 month (n=108)	2	0

[a]Including only patients who achieved castration levels of testosterone by second dose.

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