A 12-Month Clinical Study of LA-2585 (45.0 MG): A New 6-Month Subcutaneous Delivery System for Leuprolide Acetate for the Treatment of Prostate Cancer

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Purpose: The safety, efficacy and pharmacokinetics of LA-2585, a new 6-month subcutaneous depot of leuprolide acetate (Atrix Laboratories, Fort Collins, Colorado) were investigated in patients with prostate cancer.

Materials and Methods: In this 12-month, open label, multicenter study 111 patients with adenocarcinoma of the prostate were administered 45.0 mg LA-2585 subcutaneously once every 6 months. The primary efficacy parameter was serum testosterone 50 ng/dl or less. Leuprolide acetate pharmacokinetics were analyzed in a subset of 28 patients.

Results: Of the 111 enrolled patients 103 (93%) completed the 12-month study. Eight patients withdrew due to nonmedical reasons in 1, disease progression in 5 and cardiovascular disease in 2. By day 28, 108 of the 109 remaining patients (99%) achieved testosterone suppression, while 1 who never attained suppression was withdrawn at day 85. Mean time to castrate suppression was 21.2 days (median 21). At study completion 102 of 103 patients (99%) were below medical castrate testosterone levels of 50 ng/dl (mean ± SE 12.3 ± 2.1 ng/dl) with 91 of 103 (88%) at less than 20 ng/dl. Mean luteinizing hormone decreased from 6.98 ± 0.48 mIU/ml at baseline to 0.23 ± 0.14 mIU/ml at month 12. Luteinizing hormone was consistently below 1 mIU/ml. Mean prostate specific antigen decreased 97% from 39.8 ± 21.5 ng/ml at baseline to 1.2 ± 0.3 ng/ml at 12 months. No clinically significant flare reactions were observed. The most common treatment related adverse event was mild to moderate hot flashes.

Conclusions: LA-2585 (45.0 mg depot) consistently produced and maintained safe and effective serum testosterone suppression with total serum testosterone well below the medical castrate level of less than 50 ng/dl.

Key Words: prostate, clinical trials, prostate cancer, leuprolide, prostate-specific antigen

Testosterone suppression remains the standard palliative treatment in men with advanced prostate cancer and it is most commonly achieved by the administration of an LHRH analogue. Originally LHRH agonist treatment required daily subcutaneous injections. However, 1, 3, 4 and 12-month delivery systems have been developed in the last decade. These long-term delivery systems have greatly contributed to physician use of and patient compliance with this therapy.[1] Nevertheless, patients who travel or are evaluated once every 3 months would benefit from a formulation that extends treatment to once every 6 months.

LA-2585 (45.0 mg) is a newly developed, extended release, subcutaneous formulation of LA that is designed to deliver 45.0 mg of this well accepted LHRH agonist during a 6-month (168-day) period. The delivery system contains a uniquely formulated, biodegradable polymer of D, L-lactide-co-glycolide dissolved in N-methyl-2-pyrrolidone. After LA is mixed with the delivery system the formulation is injected as a liquid, forming a solid subcutaneous depot that releases leuprolide acetate during a 6-month period. We investigated the safety, pharmacokinetics and efficacy of LA-2585 administered at 6-month intervals in patients with prostate cancer.

MATERIALS AND METHODS

The study was a 12-month, multicenter, open label, fixed dose investigation of a single 45 mg dose of the study drug formulation given every 6 months for a total of 2 injections. We determined the safety and efficacy of the proposed 6-month formulation in patients with prostate cancer.

Subjects. Patients were screened after providing institutional review board approved informed consent. Participants were required to have a histological or cytological diagnosis of prostate adenocarcinoma, (greater than stage T1), a WHO

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performance score of 0 to 2 and a life expectancy of at least 1 year. Patient exclusion criteria were serum testosterone less than 150 ng/dl at screening, prostate cancer therapy within 2 months of baseline (eg radiation, immunotherapy and tumor vaccines), prostatic surgery less than 2 weeks prior to baseline, hormone therapy within 3 months of baseline (eg leuprolide acetate, goserelin acetate, bicalutamide, etc), hypersensitivity to LHRH agonists, requirement for adjuvant cancer therapy (eg radiation, chemotherapy and antiandrogen therapy), urinary tract obstruction, spinal cord compression, brain metastases, serious cardiovascular disorders or procedures within 6 months of baseline, insulin dependent diabetes mellitus, prior orchiectomy, hypophysectomy or adrenalectomy, and/or abnormal renal or hepatic function.

Study drug. LA-2585 (45.0 mg depot) consists of a delivery system that includes a sterile polymer formulation of poly (D, L-lactide-co-glycolide) and N-methyl-2-pyrrolidone in 1 syringe and lyophilized sterile LA in a second syringe. The syringes were joined via Luer-Lok® connections and the contents were passed between the syringes until thoroughly mixed. The product (0.375 ml) was then injected subcutaneously with a -inch, 19 gauge hypodermic needle into the upper right or upper left abdominal quadrant.

Procedures. All patients were to receive 45.0 mg LA-2585 at 6-month intervals, ie at baseline and on day 168. Blood samples were collected and assayed for testosterone, LH, PSA and total acid phosphatase at the initial screening, at baseline and at regular intervals throughout the 12-month study. A total of 28 patients had additional blood samples taken for PK analysis of serum LA.

Safety was determined by clinical adverse event information, clinical laboratory values (eg hematology, coagulation and serum chemistry) and vital signs. The primary efficacy outcome was a decrease in total serum testosterone to 50 ng/dl or less on at least 2 consecutive measurements taken 1 week apart. Onset of castrate suppression was defined as the first of these 2 time points. A breakthrough response was defined as a single serum testosterone value increasing above 50 ng/dl after castrate suppression. Patient self-assessment of bone pain, urinary pain and urinary symptoms was determined throughout the study using a visual analog scale with no pain or no difficulty scored as 1 and worst possible pain or very difficult scored as 10.

Baseline characteristics

Characteristics	
No. pts	111
Mean age ± SE (range)	73.2 ± 7.5 (50–86)
No. age groups (%):	
50–59	6 (5.4)
60–69	25 (22.5)
70–79	55 (49.6)
80–86	25 (22.5)
No. ethnic group (%):	
White	84 (75.7)
Black	19 (17.1)
Hispanic	6 (5.4)
Asian	1 (0.9)
Other	1 (0.9)
No. Jewett stage (%):	
A	5 (4)
B	43 (39)
C	19 (17)
D	44 (40)

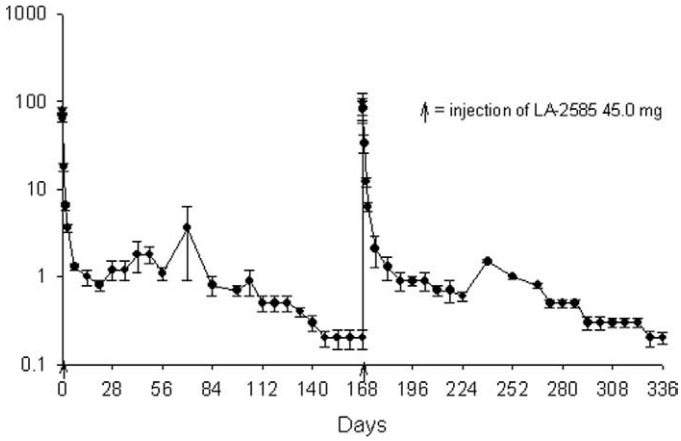

FIG. 1. Mean serum LA ± SEM from subcutaneous injections of LA-2585 (45.0 mg depot) given at 6-month (168-day) intervals during 12-month period in 28 subjects at day 168 and 6 at day 336.

Patient blood samples were analyzed elsewhere for hematology, coagulation and serum chemistry. Testosterone and LH were determined by radioimmunoassay elsewhere and LA was determined by mass spectrometry elsewhere. Lower limits of quantitation for the assays were testosterone 3 ng/dl, LH 0.02 mIU/ml and LA 0.05 ng/ml. All assays had interassay and intra-assay percent coefficients of variability of less than 20.

Descriptive statistics were used to summarize concentrations at each time point, and mean and median time to testosterone suppression. Values, which were determined using SAS, version 8.1 (SAS Institute, Cary, North Carolina), are reported as the mean ± SE. Patients with baseline data only, ie no on-study efficacy data, were not included in the analysis. The last data point from each of the 8 patients who voluntarily withdrew was carried forward.

RESULTS

A total of 22 centers were involved in the study with a mean of 5.0 ± 0.8 subjects (range 1 to 16). All data were pooled across centers for statistical analyses. Of the patients 111 received the first injection and 106 received the second injection. Of the original 111 patients 103 completed the 12-month study and 73 had no missing data points. Eight patients withdrew from the study due to nonmedical reasons in 1, disease progression in 5 and cardiovascular disease in 2, including fatal myocardial infarction and stroke in 1 each. The table lists baseline demographic and disease status data.

In the PK group 26 of 28 patients (92.9%) completed the study and received the 2 injections. One patient was excluded due to omission of the PK sample collection and 1 who received only the first injection was included in first injection data. Patient demographics were similar between the PK and study populations. PK data showed an initial release of LA after each injection with C_{max} serum values of 82.0 ± 38.2 ng/ml 4.4 ± 1.7 hours after the first injection and 102.4 ± 72.1 ng/ml t 4.8 ± 2.0 hours after the second injection (fig. 1). Serum LA then decreased slowly from days 3 to 168 (plateau phase). During the plateau phase mean serum LA generally remained between 0.2 and 2.0 ng/ml with a 6-month (336-day) mean value of 0.20 ± 0.14 ng/ml (median