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A Retrospective Study Evaluating the Efficacy and Tolerability of Intra-abdominal, Once-yearly Histrelin Acetate Subcutaneous Implants in Patients with Advanced Prostate Cancer

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ABSTRACT

Introduction: Luteinizing hormone-releasing hormone (LHRH) agonists are an androgen deprivation therapy used in advanced prostate cancer. The LHRH agonist histrelin is available as an implant of histrelin acetate for once-yearly subcutaneous administration into the upper arm. A single-center, clinical retrospective chart review was performed to characterize the safety and efficacy of abdominal insertion of the histrelin acetate implant.
Methods: Data were collected retrospectively from the charts of 64 patients aged ≥ 45 years with prostate cancer who received the histrelin acetate implant subcutaneously inserted into the abdomen at a single center. Of these, 37 patients received a second implant after 1 year.
Results: Following the first implant, mean serum testosterone levels were 0.38 nmol/L (10.89 ng/dL) at 6 months (n = 19) and 0.52 nmol/L (14.96 ng/dL) at 12 months (n = 33); serum testosterone level was ≤ 1.04 nmol/L (≤ 30 ng/dL) in 94.7 and 90.9% of patients at 6 and 12 months, respectively. Mean serum prostate-specific antigen levels were 6.56 µg/L (6.56 ng/mL) at 6 months (n = 23) and 4.58 µg/L (4.58 ng/mL) at 12 months (n = 40). Efficacy was maintained in patients who received a second implant. Adverse events occurred in 3 patients. Eleven patients died during the chart review period; these deaths were deemed unrelated to histrelin acetate implant use.
Conclusion: Insertion of the histrelin acetate implant into the abdomen appears to be an effective and generally well-tolerated alternative administration method.

INTRODUCTION

Prostate cancer is a leading type of cancer among men in the United States. The American Cancer Society estimated that in 2010 there would be over 217 000 new cases of prostate cancer (representing 28% of new cancer cases in men in the U.S.) and over 32 000 deaths caused by the disease (representing 11% of cancer-related deaths) [1]. Prostate cancer growth is stimulated by testosterone, and androgen deprivation therapy (ADT) is frequently used for the treatment of advanced prostate cancer. Androgen deprivation therapy may be achieved surgically (bilateral orchiectomy) or by medical means, including via administration of luteinizing hormone-releasing hormone (LHRH) agonists [2].

Following an initial transient flare in testosterone levels

KEYWORDS: histrelin acetate, implant, prostate cancer, subcutaneous

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following initiation of LHRH agonist therapy [2,3], patients attain castration level within approximately 3 weeks of commencing therapy [3]. The achievement of a serum testosterone level < 1.21 to 1.74 nmol/L (< 35 to 50 ng/dL) is considered adequate for patients with prostate cancer [2,3]. LHRH agonists are a mainstay of therapy for patients with advanced prostate cancer [4]. The decision to initiate ADT should be made individually for each patient after considering all relevant clinical risk factors [4].

The LHRH agonist histrelin is available as a sustained-release hydrogel implant of histrelin acetate for once-yearly administration [5]. The histrelin acetate implant is 3.5 cm long by 3 mm in diameter and is administered subcutaneously into the inner aspect of the upper arm in a minor in-office surgical procedure [5]. In the pivotal open-label, single-arm study of the histrelin acetate implant in 138 patients with prostate cancer, mean serum testosterone showed minimal flare at week 1; in addition, serum testosterone levels were reduced to < 1.74 nmol/L (< 50 ng/dL) (indicative of medical castration) in all evaluable patients by week 4, and suppression was maintained for 52 weeks in > 99% of patients [6]. In an extension of this study, in which patients received once-yearly histrelin acetate implants, testosterone levels were maintained at < 1.74 nmol/L (< 50 ng/dL) for up to 208 weeks [7].

The histrelin acetate implant has been studied when placed in the inner aspect of the upper arm, but its placement in other sites has not been formally evaluated. The purpose of this retrospective chart review was to characterize the safety and efficacy of the histrelin acetate implant when placed in the abdomen.

METHODS

Subjects and Treatment

Data were collected retrospectively during the period of June 2007 to August 2009 from the charts of all patients who received the histrelin acetate implant inserted into the abdomen at a single center. Patients included in the analysis were aged ≥ 45 years, had a diagnosis of prostate cancer, and were deemed appropriate candidates for ADT.

Patients received histrelin acetate delivered using a sterile, diffusion-controlled reservoir drug delivery system (VANTAS; Endo Pharmaceuticals, Chadds Ford, PA, USA). The implant contains a 50 mg histrelin acetate drug core inside a nonbiodegradable cylindrical hydrogel reservoir and releases the drug at ~50 µg/day [5]. During an aseptic office-based surgical procedure, the histrelin acetate implant was inserted subcutaneously into the abdominal area approximately 2 fingerbreadths below the costal margins in the mid-axillary (nipple) line, and roughly in-line with an inferior/superior line at the proximal aspect of the iliac crest, using the insertion device supplied with the implant.

Statistics

Qualitative data are presented as the number of patients and the percentage of the total population. Quantitative data are summarized using descriptive statistics, including mean, standard deviation (SD), and standard error.

RESULTS

Retrospective chart data were analyzed from 64 patients. The mean (± SD) age was 78.4 (10.7) years, mean (± SD) weight was 89.0 (18.3) kg, and mean (± SD) height was 174.0 (5.8) cm. Of the 42 patients for whom race was recorded, 37 (88.1%) were Caucasian, 4 (9.5%) were African American, and 1 (2.4%) was Hispanic. The majority of patients (38/64; 59.4%) had been treated with LHRH agonist therapy prior to administration of the histrelin acetate implant, with the most common agent being leuprolide acetate. Among the 58 patients with available serum prostate-specific antigen (PSA) levels prior to administration of the histrelin acetate implant, the mean level was 9.13 µg/L (9.13 ng/mL), and 26 of 58 patients (44.8%) had PSA levels ≥ 5 µg/L (≥ 5 ng/mL). Among the 16 patients with available serum testosterone levels prior to administration of the histrelin acetate implant, the mean level was 2.65 nmol/L (76.43 ng/dL), and 7 out of 16 patients (43.8%) had testosterone levels ≤ 1.04 nmol/L (≤ 30 ng/dL). The patients receiving prior LHRH agonist therapy in the chart review population received the histrelin acetate implant at the prescribed end of their prior LHRH agonist administration, and continued LHRH agonist therapy was indicated. The testosterone levels in these patients were subject to the clinical variability in the waning of the therapeutic effect from previous depot injection formulations (clinical observation).

A total of 37 patients received a second implant after 1 year, 11 patients died, the implant was not removed from 6 patients, and 1 patient discontinued therapy for financial reasons. None of the deaths were judged to be related to use of the histrelin acetate implant. Nine patients did not receive a second histrelin acetate implant for reasons that included not being implanted to downstage their prostate cancer prior to radiation therapy, requesting intermittent ADT, and not wishing to have ADT.

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Figure 1. Mean (± standard error) serum testosterone levels during one year following the first histrelin acetate implant, and during a second year in patients receiving a second implant. To convert ng/dL to nmol/L, multiply by 0.0347.

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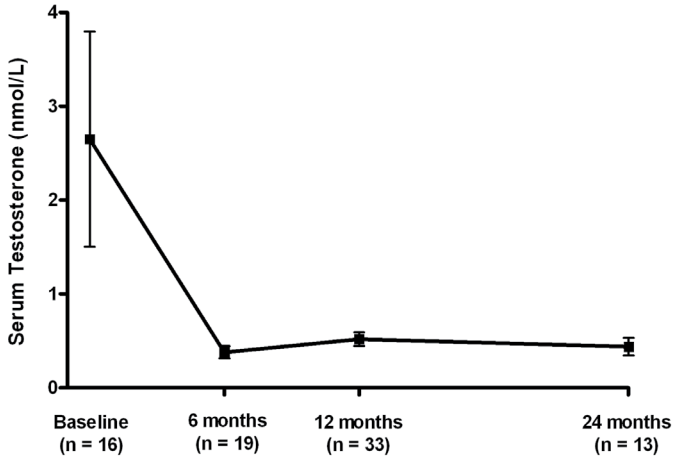

Figure 2. Mean (± standard error) serum prostate-specific antigen (PSA) levels during 1 year following the first histrelin acetate implant, and during a second year in patients receiving a second implant. To convert ng/mL to µg/L, multiply by 1.

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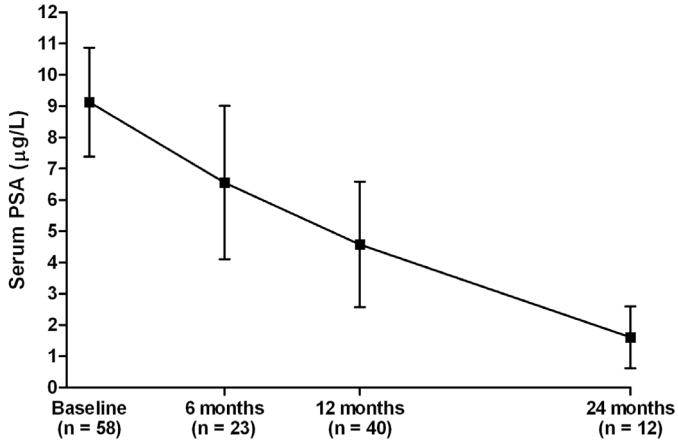

Efficacy

Following insertion of the first implant into the abdomen, the mean serum testosterone level was 0.38 nmol/L (10.89 ng/dL) at 6 months (n = 19) and 0.52 nmol/L (14.96 ng/dL) at 12 months (n = 33; Figure 1). The proportion of patients with a serum testosterone level ≤ 1.04 nmol/L (≤ 30 ng/dL) was 94.7% (18/19 patients) at 6 months and 90.9% (30/33 patients) at 12 months. In addition, the mean serum PSA level decreased to 6.56 µg/L (6.56 ng/mL) at 6 months (n = 23) and 4.58 µg/L (4.58 ng/mL) at 12 months (n = 40; Figure 2).

Continued efficacy was seen in patients who received a second implant at 1 year. The mean serum testosterone level at 2 years was 0.44 nmol/L (12.76 ng/dL) (n = 13; Figure 1), with all 13 patients assessed at this time point having a serum testosterone level ≤ 1.04 nmol/L (≤ 30 ng/dL). The mean serum PSA level at 2 years was 1.61 µg/L (1.61 ng/mL) (n = 12; Figure 2). Among the 9 patients who had received prior LHRH agonist therapy and had serum testosterone levels recorded, 7 patients had a decrease and 2 patients had an increase from baseline in this parameter.

Safety

At the time of re-implantation, the previous implant could not be located for removal in 4 patients, and in 1 additional patient ultrasound was used to locate the implant. In another 4 patients, the clinical decision was made not to remove the previous implant. In 1 patient, the implant was reinserted after unintended expulsion < 1 month after insertion. Subsequent clinical follow-up on this patient indicated maintenance of androgen suppression.

Three patients experienced adverse events: in 1 patient, the second implant protruded through the skin approximately 14 months after implantation and was replaced; 1 patient experienced redness and irritation around the implant removal site; and 1 patient experienced pain at the implant site 1 week after implantation (considered to be due to a muscle strain and unrelated to the implant) and hot flashes. Eleven patients included in this analysis died after ≥ 1 year of evaluation; none of the deaths were deemed related to use of the histrelin acetate implant.

DISCUSSION

There is clinical interest in the suitability of the abdomen as an alternative insertion site for the VANTAS implant, as this site may incur less irritation and environmental contamination. The main finding of this retrospective chart review is that implantation of the histrelin acetate implant into the abdomen instead of the upper arm appears to be effective at reducing serum testosterone to anorchid levels and is well tolerated in patients with advanced prostate cancer.

The patient population reviewed was similar to that enrolled in the pivotal study evaluating the histrelin acetate implant [6]. In the current analysis, the mean age was 78 years, 88% of patients were Caucasian, and 45% had a PSA level ≥ 5 µg/L (≥ 5 ng/mL). A major difference was that approximately 60% of patients in the current chart review had previously received an LHRH agonist. Interestingly, the pivotal study reported by Schlegel excluded patients who had undergone bilateral orchiectomy or had received hormonal agents (including androgen receptor blockade, androgen ablative therapy, or systemic corticosteroid therapy) in the previous year [6].

The current chart review demonstrated that following subcutaneous administration of the histrelin acetate implant in the abdominal area (as described) mean serum testosterone was reduced to below castration levels (< 1.74 nmol/L [< 50 ng/dL]), with mean values of 0.38 nmol/L (10.89 ng/dL) and 0.52 nmol/L (14.96 ng/dL) at 6 and 12 months, respectively. These levels are similar to those reported by Schlegel and colleagues in the pivotal study in which the histrelin acetate implant was inserted into the upper arm [6]. All of the 134 evaluable patients in the Schlegel study attained chemical castration by week 4, and over 99% of patients maintained this throughout the 52-week study duration [6]. In the current chart review, 90.9% of patients achieved chemical castration in the first year, and 100% of patients who received a second implant after 1 year achieved chemical castration at 2 years. In this population, continuous and uninterrupted long-term ADT may be clinically important. Furthermore, the results of the chart review support other recently reported data [7], which show that androgen suppression is maintained with the histrelin acetate implant over successive yearly cycles of insertion and removal without interruption following reimplantation.

The corresponding decrease in serum PSA levels was similar in patients receiving the histrelin acetate implant in the abdomen compared with those who received the implant in the upper arm. In the current chart review, mean serum PSA level was 6.56 µg/L (6.56 ng/mL) at 6 months and 4.58 µg/L (4.58 ng/mL) at 12 months. In the Schlegel study, the mean serum PSA level was 4.43 µg/L (4.43 ng/mL) at 16 weeks [6]. Histrelin acetate appeared to be active in patients who had received prior LHRH agonist therapy, and thus may represent a treatment option in patients unresponsive to or intolerant of previous LHRH agonist therapy, or who prefer an agent that is administered once yearly.

Intra-abdominal administration of histrelin acetate was well tolerated by the patients represented in the current chart review, with minimal adverse events reported. The adverse events that occurred were insertion site reactions and hot flashes. These adverse events are similar to those previously reported with insertion of the histrelin acetate implant into the arm [6].

CONCLUSIONS

This retrospective chart review indicates that subcutaneous insertion of the histrelin acetate implant into the abdomen, as an alternative method to subcutaneous insertion into the inner aspect of the upper arm, is effective at reducing serum testosterone below castration levels and reducing serum PSA levels. This alternative technique also appears to be generally well tolerated.

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Sean Woolen, Knox Beasley, and Joseph Zahn declare no conflicts of interest.

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