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A NEW LONG ACTING FORMULATION OF THE LUTEINIZING HORMONE-RELEASING HORMONE ANALOGUE, GOSERELIN: RESULTS OF STUDIES IN PROSTATE CANCER

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ABSTRACT

Purpose: To assess the pharmacodynamic equivalence of the new 10.8 mg. goserelin depot with the current 3.6 mg. depot 3 studies were performed in patients with advanced prostate cancer.

Materials and Methods: In 2 comparative studies 160 patients were randomized for dosing every 12 weeks using the 10.8 mg. depot or every 4 weeks using the 3.6 mg. depot. In the noncomparative study 35 patients received the 10.8 mg. depot. Blood sampling for serum testosterone and evaluation of toxicity was done during the 48-week study period.

Results: Serum testosterone profiles of the 10.8 and 3.6 mg. goserelin depots were similar with testosterone levels decreasing into the castrate range by day 21 after depot administration. The safety profile of 10.8 mg. goserelin is comparable to that of the current monthly depot with the main side effects related to androgen deprivation.

Conclusions: The new long acting depot was pharmacologically equivalent, and well tolerated locally and systemically, and will offer added convenience to patients and health care personnel.

KEY WORDS: prostate, prostatic neoplasms, testosterone, goserelin, delayed-action preparations

Prostate cancer is now the most common newly diagnosed malignancy in men in the United States with an estimated 200,000 new diagnoses and 38,000 deaths in 1994.[1] It predominantly affects the elderly male population, which has contributed to an increasing incidence in recent years. The established mode of treatment of advanced disease is androgen deprivation. The development of luteinizing hormone-releasing hormone analogues has offered an effective and well tolerated pharmacological alternative to orchiectomy, while the availability of depot formulations has contributed to the rapid establishment of this class of compounds in the treatment of this disease.

Currently available depot formulations of luteinizing hormone-releasing hormone analogues require administration by injection subcutaneously or intramuscularly on a monthly basis, which usually involves a clinic visit by a patient or a home visit by health care personnel. A longer acting depot formulation would reduce the frequency of injections and offer improved convenience to patients and health care personnel. The luteinizing hormone-releasing hormone analogue, goserelin,‡ is currently available as a depot containing 3.6 mg. goserelin acetate administered by subcutaneous injection every 28 days. A new 10.8 mg. formulation has been developed based on modifications of the lactide:glycolide copolymer carrier of the current 3.6 mg. dose, containing 10.8 mg. goserelin acetate designed to be administered every 12 weeks. We performed 1 noncomparative and 2 comparative studies with this depot in patients with prostate cancer to assess its pharmacodynamic equivalence with the current 3.6 mg. depot.

MATERIALS AND METHODS

Population. Between January 1989 and July 1992, 195 patients with advanced prostate cancer were entered by the Dutch South East Cooperative Urological Group into the 3 studies, including 80 into each of the 2 comparative studies and 35 into the noncomparative study. Patients with histological confirmation of prostate cancer, locally advanced (T3 to T4) or metastatic (M1) disease, pretreatment serum testosterone within the normal range and life expectancy of more than 6 months were eligible for entry into the study, and those previously treated with orchiectomy or hormonal therapy were excluded. All patients provided informed consent. After study entry patients were withdrawn because of a serious adverse event, disease progression requiring change of treatment, unwillingness or inability to continue in the study or investigator decision in the interest of the patient.

Design and assessments. Multicenter comparative studies 1 and 2 were of an identical open, parallel group design with a 48-week study period. Patients were randomized to receive treatment with a single 10.8 mg. goserelin depot or 3 consecutive monthly 3.6 mg. goserelin depots during weeks 0 to 12. Following this period all patients received treatment with a single goserelin 10.8 mg. depot every 12 weeks. Blood sampling for serum testosterone was performed before randomization, at weekly intervals for the first 4 weeks, then every 2 weeks until week 24, and at the end of weeks 36 and 48. On days when sampling coincided with depot administration samples were taken before the depot was given. Samples were analyzed centrally at the laboratories of University Hospital, Nijmegen. Patients in noncomparative pharmacokinetic study 3 received a single 10.8 mg. goserelin depot. Blood sampling for serum testosterone was performed before treatment on day 1, then on days 2, 3, 5 and 8, followed by weekly sampling until 2 consecutive samples had been obtained with serum testosterone levels exceeding at least twice the upper limit of the castrate range (0 to 2.5 nmol./l.).

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TABLE 1. *Demographic details*

	Comparative				Noncomparative Study 3
	Study 1		Study 2		
Depot (mg.)	10.8	3.6	10.8	3.6	10.8
No. pts.	38	42	39	41	35
Mean age (range)	72 (55–86)	73 (56–89)	73 (49–88)	71 (52–86)	72 (53–86)
Mean kg. wt. (range)	80 (53–100)	76 (48–105)	74 (57–105)	77 (54–108)	73 (45–91)

Response criteria. The primary objective of the studies was to assess pharmacodynamic equivalence of the 10.8 mg. goserelin depot with the current 3.6 mg. depot. Therefore, the main end point was the surrogate end point of serum testosterone. In the comparative studies this end point was assessed in 2 ways. Mean testosterone levels achieved during weeks 4 to 12 and at the end of weeks 4, 8 and 12 were statistically compared between the 10.8 and 3.6 mg. treatment groups. In addition, serum testosterone levels of individuals were assessed according to criteria for induction, as defined by testosterone levels decreasing into the castrate range within 28 days of first administration, and maintenance, as defined by serum testosterone levels remaining within the castrate range throughout a 12-week dosing period.

Statistical methods. Analysis of variance was done to compare mean testosterone levels among weeks 4 to 12 of the 2 comparative studies separately and pooled. Possible sources of variation of study, center within study, treatment, and study and center by treatment interaction were considered. Induction and maintenance data were summarized in terms of numbers of patients meeting the criteria. Successful induction required that at least 1 sample value be within the castrate limit within 28 days of the first depot administration. For successful maintenance all patients who received at least 1 depot were required to have no sample levels outside of the castrate range within 84 days of depot administration, excluding the induction period for the first depot. A 95% confidence interval was derived for the difference in percent maintenance rates between the 2 treatment groups to assess the precision of comparison. Induction and maintenance success results of the noncomparative study were analyzed similarly.

RESULTS

Demography. Patients in each of the comparative studies were comparable in age and weight (table 1). There were 3 protocol deviators in study 2. Two patients randomized to the 3.6 mg. group received a 10.8 mg. depot in error at week 8. The testosterone data from week 8 were excluded from efficacy analysis, while they were included in the 10.8 mg. group during this period for safety assessments. One patient randomized to the 10.8 mg. depot received a 3.6 mg. depot in error at week 0 and no further depots until week 12. This patient was excluded from efficacy analysis but was included in the 3.6 mg. depot group for safety assessment during this period.

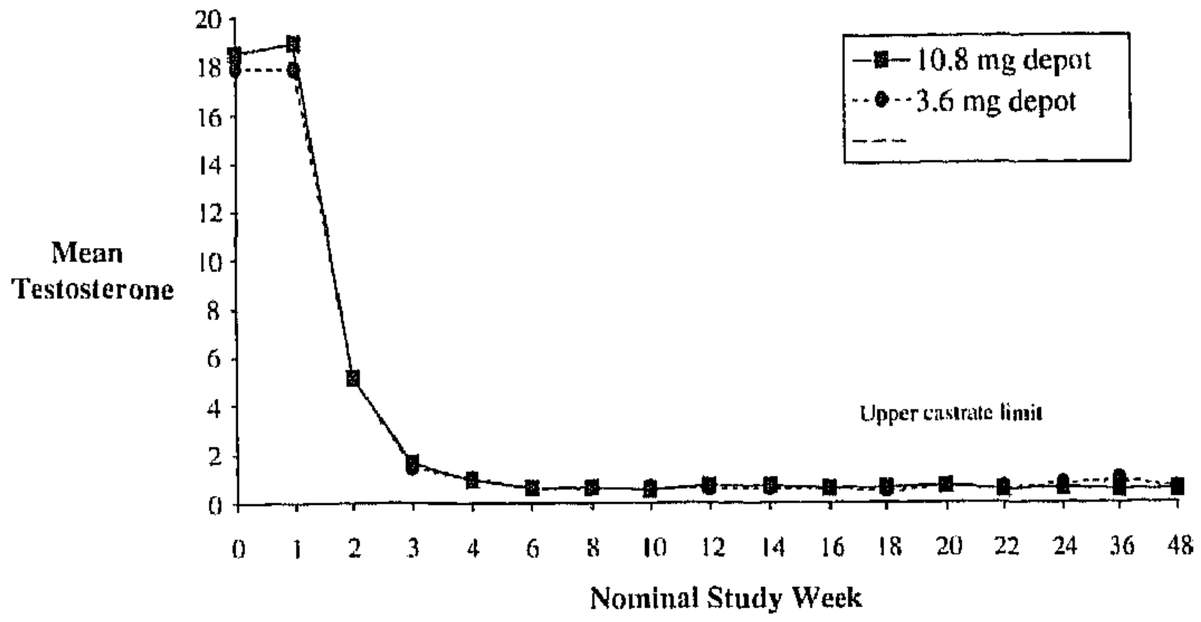
Mean serum testosterone levels. In studies 1 and 2 mean testosterone levels during weeks 4 to 12, and 4, 8 and 12 were within the castrate range with no significant differences between the 10.8 and 3.6 mg. treatment groups. Pooling data from the 2 studies indicated that there were no significant differences in mean testosterone levels achieved by the 2 depot formulations (table 2). The figure shows the mean serum testosterone profile achieved in the 2 treatment groups pooled from both comparative studies. Between weeks 0 and 12 the profiles relate to the 10.8 and 3.6 mg. depots, while between weeks 12 and 48 patients in both treatment groups received 10.8 mg. goserelin depots. The achieved profiles were similar with testosterone levels decreasing into the castrate range by day 21 after administration of the first depot in each group, and then remaining within the castrate range for the remainder of the period, ending at week 12. On repeat dosing of 10.8 mg. goserelin beyond week 12 testosterone levels in both groups were maintained within the castrate range (see figure).

In the comparative studies all patients receiving either depot had successful induction. Following induction a similar maintenance of suppression of testosterone levels occurred in patients treated with the 10.8 and 3.6 mg. depots. As expected with this drug class, the most common adverse events were related to the pharmacological action of testosterone deprivation. The incidence of such events during the comparative studies is shown in table 3. The most commonly reported event was hot flashes, followed by gynecomastia (3 patients in the 10.8 and 1 in the 3.6 mg. group), breast pain (2 and 1, respectively), impotence (2 in the 10.8 mg. group) and bone pain (2 in each group). The incidence of these events during treatment with 10.8 mg. goserelin was comparable to that after treatment with the 3.6 mg. goserelin depot. The incidences beyond week 12 reflect the differences in the periods of observation and recording of events that persisted beyond week 12.

Only 1 patient had an adverse event that led to study withdrawal. In study 2, 1 patient had mild pruritis from paraneoplastic dermatitis unrelated to goserelin use. No patient was withdrawn from the study due to an adverse event related to treatment. The incidence of early worsening of signs and symptoms was similar for patients treated with 10.8 and 3.6 mg. goserelin depots. Pain/bone pain increased in 4% of patients in each treatment group and there was 1 case of spinal cord compression in each group. One patient had medullary compression 8 days after the first 3.6 mg. goserelin depot, while 1 had spinal cord compression on the

TABLE 2. *Mean serum testosterone levels in comparative studies*

	10.8 Mg. Depot (nmol./l.)	No. Pts.	3.6 Mg. Depot (nmol./l.)	No. Pts.	Estimated difference (nmol./l.)	95% Confidence Interval	p Value
Study 1 (wks.):							
4 to 12	0.559	37	0.632	42	−0.033	−0.294–0.228	0.8043
4	0.822	35	1.101	39	−0.279	−1.312–0.755	0.5919
8	0.672	34	0.531	36	0.140	−0.083–0.364	0.2143
12	0.753	33	0.564	36	0.189	−0.086–0.464	0.1747
Study 2 (wks.):							
4 to 12	0.681	39	0.743	38	−0.062	−0.199–0.075	0.3704
4	0.776	38	0.782	37	−0.006	−0.118–0.176	0.9456
8	0.653	36	0.721	36	−0.068	−0.257–0.122	0.4763
12	0.786	36	0.664	35	0.121	−0.139–0.381	0.3550
Pooled data (wks. 4 to 12)	0.639	76	0.686	80	−0.047	−0.193–0.099	0.5264



Mean serum testosterone levels during 48 weeks in studies 1 and 2

TABLE 3. *Adverse events*

	Wks. 0 to 12		Wk. 12 Onward
Depot (mg.)	10.8	3.6	10.8
No. pts.	78	84	157
% Adverse events:			
Hot flashes	47.4	47.6	63.7
Gynecomastia	3.8	1.2	8.3
Breast pain	2.6	1.2	4.5
Impotence	2.6	0	1.3
Bone pain	2.6	2.4	5.7

day of the first 10.8 mg. goserelin depot, which was considered by the clinician to be related to disease progression. Three cases of urinary retention in the 3.6 mg. group were treated successfully with urinary catheterization, and there were no such cases in the 10.8 mg. group. No deaths were considered related to treatment. Depots of 10.8 mg. goserelin were well tolerated locally, and only 2 of the 614 depot administrations (0.3%) in the comparative studies were associated with local reactions (hematomas not requiring specific management).

DISCUSSION

Randomized comparative studies on the use of luteinizing hormone-releasing hormone analogues in patients with advanced prostatic carcinoma have clearly established that these substances suppress serum testosterone into the castrate range. This suppression is maintained on repeat dosing, and is associated with clinical responses and survival times similar to those achieved with orchiectomy and estrogens.[2,3] Luteinizing hormone-releasing hormone analogues are now generally accepted as a medical alternative to orchiectomy.

It is important to discuss with every patient the best way in which testosterone suppression can be achieved. The major point of discussion is whether surgical or medical castration should be performed. The choice of medical or surgical castration should not depend solely on economic reasons. The psychological impact and consequences of surgery should also be considered, in addition to the irreversibility of the intervention.

There exist only limited prospective data in regard to patient preference and it is surprising how little attention has been given to patient attitude in this respect. Chadwick et al concluded that with equally effective treatments a fully informed patient should be encouraged to participate in deciding the treatment (surgical or medical castration) he should receive.[4] The study indicated that inpatients were more inclined to elect surgical castration, whereas outpatients preferred luteinizing hormone-releasing hormone therapy. In a Norwegian study patients clearly preferred luteinizing hormone-releasing hormone depot therapy, which was also the treatment that Norwegian urologists would prefer for themselves.[5] Cassileth et al suggested that luteinizing hormone-releasing hormone depot therapy may be superior to surgical castration in terms of long-term improvement of quality of life and psychological distress,[6] although a significant statistical difference in quality of life parameters was not demonstrated in the study of Parmar et al.[7]

The administration of luteinizing hormone-releasing hormone analogues evolved from daily intranasal or subcutaneous application to monthly depot injections, which are considered more convenient for patients. An initial depot preparation was the 3.6 mg. goserelin subcutaneous depot, which is administered monthly and has proved to be effective in suppressing testosterone in all patients with advanced prostatic cancer.[8] However, even a monthly depot preparation requires frequent visits by patients, which for some elderly individuals can be embarrassing and cumbersome. Therefore, it would be advantageous for patients and physicians or other health care personnel if a longer acting luteinizing hormone-releasing hormone depot preparation were available with an administration frequency that coincided with regularly scheduled treatment for advanced metastatic prostate cancer. In general, a 3-month depot preparation was considered the most appropriate formulation.

CONCLUSIONS

We evaluated the pharmacological equivalence of a new 3-month 10.8 mg. goserelin depot with the current 3.6 mg. depot, as demonstrated by a similar testosterone profile. Induction and maintenance rates during the prolonged dosing period of 12 weeks were comparable to those of the current 3.6 mg. depot, which is given at 28-day intervals. The safety profile of the new depot was also similar to that of the current depot with a similar incidence of pharmacologically related adverse events. The depot was well tolerated with no patient study withdrawals related to treatment. There was also a similar incidence of early worsening of signs and symptoms in some patients shortly after administration of the first depot. The new depot will provide a significant reduction in the number and frequency of injections, which should lead to improved convenience for patients and health care personnel with potential reductions in costs of depot administration.

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