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A phase II trial with new triptorelin sustained release formulations in prostatic carcinoma

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Abstract. *Objectives:* The objectives were to assess if a single intramuscular (IM) injection of the GnRH agonist triptorelin, as pamoate Sustained Release (RS) 11.25 mg, was able to induce pharmacological castration and to maintain the plasma testosterone levels in the castrate range (<1.735 nmol/l) up to 3 months in prostatic carcinoma. *Methods:* Two different formulations of triptorelin pamoate 11.25 mg were assessed in 2 groups of 10 patients suffering from prostatic carcinoma. Each patient received one IM injection of triptorelin pamoate SR 11.25 mg. Triptorelin and testosterone levels were measured over 3 months. Pain, micturition difficulties, performance status, local and general tolerance, and the occurrence of adverse events were evaluated. *Results:* Both formulations were able to induce castration levels (<1.735 nmol/l) of testosterone within 3 to 4 weeks post-injection, and to maintain levels below 1.735 nmol/l till the end of 3rd month. The bioavailability of one formulation (DLGSD-3-95-21) tended to be greater. This may explain the quicker onset of castration and the slight better maintenance of low testosterone levels during the 3rd month observed with this formulation. In terms of clinical end-points, the local tolerance of both formulations was excellent. No serious adverse events were recorded except transient hot flushes in 2 cases and slight bone pain in one. *Conclusion:* Triptorelin pamoate 11.25 mg given in microgranules is a 3-month sustained-release administration form which appears to be safe and effective in advanced prostatic carcinoma. Based on the findings of this study, the formulation with greater bioavailability (DLGSD-3-95-21) was selected as formulation of choice to be used for clinical treatments and further clinical investigation.

Key words: Hormonal therapy, Prostatic carcinoma, Triptorelin

Introduction

Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone releasing hormone (LHRH), is secreted by the hypothalamus, and stimulates both the synthesis and the release from the pituitary of the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH) [1]. LH stimulates the testes to produce testosterone, and FSH stimulates spermatogenesis.

Hypothalamic release of GnRH and its action on the pituitary are controlled by bio-feedback mechanisms based on the amount of sex steroid hormones in the circulation. However the chronic and continuous stimulation of LH secretion by either repeated administration of GnRH or single administration of long acting GnRH agonists results in desensitization of gonadotropin secretion and induces pharmacological castration in man.

Natural GnRH has a short duration of action [2]. Synthetic peptide analogues of GnRH have been developed with improved potency and prolonged duration of action. They induce the marked decrease of the testicular secretion and are a first intention treatment of advanced prostatic carcinoma [3]. However, initially, GnRH analogues produce stimulation of LH and FSH production with a rise of testosterone lasting some days followed by a falling pattern within 1 to 2 weeks. An achievement of castration levels is normally obtained within one month [4, 5]. The initial rise in testosterone may cause an increase of bone pain within the first days of treatment. For this reason GnRH analogues cannot be used alone in patients with life-threatening metastases (e.g. suspicion of spinal cord compression, lung or brain metastases) [6, 7, 8].

Among long-acting preparations of GnRH analogues, one of the best known in Europe is triptorelin

acetate (Decapeptyl®) which was designed to deliver medication over one month.

To allow more flexibility for practical use, a new sustained-release preparation of triptorelin pamoate 11.25 mg in microgranules has been developed (Debiopharm SA, CH-1003 Lausanne, Switzerland). In comparison with triptorelin acetate, the advantages of triptorelin pamoate in microgranules are: 1) to be prepared without organic solvent; 2) to be stored at room temperature; 3) an easier reconstitution with water for injection; and, 4) a duration of therapeutic effect of 3 months. We report the results of an open study to determine the efficacy, safety and tolerance of two new triptorelin sustained release formulations in patients suffering from prostatic carcinoma.

Material and methods

Objectives of the study

Main objective: to determine if a single IM injection of triptorelin pamoate SR 11.25 mg was able to induce pharmacological castration and to maintain the plasma testosterone levels in the castrate range (< 1.7 nmol/l) up to 3 months in patients with prostatic carcinoma. Secondary objectives: improvement of pain, dysuria, and of the performance status; local (injection site) and general tolerance (occurrence of adverse events).

Patients

Over a 7-month period, 20 patients suffering from prostatic carcinoma, stages 1 to 4, were recruited (Section of Urology, Scientific Institute N. I. Pirogov, BG-1606 Sofia, Bulgaria). All patients gave their informed consent to the study which had been approved by the Ethics Committee of the Medical Academy of Bulgaria.

The inclusion criteria were: age > 50 years; histologically proven prostatic carcinoma; prostatic cancer which needed GnRH agonists; testosterone level > 6.0 nmol/l (1.72 ng/ml); and, expected survival > 6 months. The exclusion criteria were: orchiectomy; prior hormonal treatment for prostatic carcinoma (e.g. estrogen therapy, steroids, other GnRH agonists); brain or vertebral metastases; debilitating metabolic, renal, liver or cardiovascular disease; and, second malignancy.

Study design

This was an open, non-randomized, single-centre study. The duration of the study period was 3 months: day 0 was the first day of the treatment, day 84 the last one. The patients were hospitalized at least for the first 4 days and were subsequently evaluated as outpatients at weekly intervals till day 84.

Triptorelin pamoate SR 11.25 mg was available in 2 formulations: batch DLGSD-3-95-21 (triptorelin pamoate 11.25 mg : l/l : polymer lactide 75 : glycolide 25 [= 11.25 mg]); batch DLGSD-3-95-22 (triptorelin pamoate 11.25 mg : 1/3 : polymer lactide 50 : glycolide 50 [= 3.75 mg], and 2/3 : polymer lactide 75 : glycolide 25 [= 7.5 mg]). The medication was reconstituted with 2 ml water for injection and administered as a single IM injection (buttock) of 11.25 mg on day 0.

Patients were divided in two treatment groups: patients 1 to 10 received formulation batch DLGSD-3-95-21, and patients 11 to 20 were given formulation batch DLGSD-3-95-22. During the study, chemotherapy, steroids, estrogen therapy or other GnRH agonists were not permitted. If necessary, analgesics were authorized.

Blood samples for the triptorelin and testosterone determinations were drawn on days 0, 1, 2, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 84. Testosterone levels were measured by radioimmunoassay using commercial kit (Orion® reagents). The intra- and interassay coefficients of variation were below 8 percent within the normal male range, and 8 and 8.5 percent respectively at the level 2 nmol/l. The detection limit was 0.27 nmol/l. Triptorelin was measured by radioimmunoassay [9]. Blood samples were also drawn on days 1 and84 for standard hematology and clinical chemistry. Prostatic acid phosphatase, prostate-specific antigen, LH and FSH were not measured.

The clinical evaluation included an assessment of the intensity of bone pain as measured by the patient on a 100-mm visual-analogue scale (VAS) [10], questioning about micturition difficulties and an evaluation of the performance status on days 0 and 84. In addition, local tolerance at the injection site, possible occurrence of adverse events and changes in biological parameters were evaluated. No statistical analysis was performed and only descriptive statistics were used.

Table 1. Clinical features

Case	Age	Duration of disease (yr)	Clinical features of prostatic cancer[1]	Histopathology of prostatic carcinoma	Staging[2]	Treatment before triptorelin
Group 1: formulation DLGSD-3-95-21						
1	76	3	none	well differentiated	$T_3N_0M_0$	transurethral resection of prostate (TURP)
2	56	1	pain due to bone metastasis, urinary retention	poorly differentiated	$T_4N_1M_1$	permanent catheter
3	58	5	dysuria, pollakyuria, nocturia, pain due to bone metastasis	moderately differentiated	$T_3N_1M_1$	none
4	78	2	dysuria, nocturia	poorly differentiated	$T_3N_0M_0$	none
5	83	3	urinary retention	moderately differentiated	$T_4N_1M_0$	permanent catheter
6	63	1	urinary retention	poorly differentiated	$T_4N_1M_0$	none
7	67	1	none	well differentiated	$T_2N_0M_0$	adenomectomy
8	75	5	dysuria, pollakyuria	moderately differentiated	$T_3N_0M_0$	TURP
9	76	1	none	moderately differentiated	$T_3N_0M_0$	TURP
10	64	1	none	moderately differentiated	$T_4N_1M_0$	TURP
Group 2: formulation DLGSD-3-95-22						
11	73	10	none	well differentiated	$T_1N_0M_0$	adenomectomy
12	73	1	none	well differentiated	$T_2N_0M_0$	TURP
13	75	6	urinary retention	moderately differentiated	$T_2N_1M_1$	permanent catheter
14	70	1	none	moderately differentiated	$T_1N_0M_0$	adenomectomy
15	68	2	dysuria, nocturia	poorly differentiated	$T_3N_1M_0$	none
16	68	5	dysuria, pollakyuria, nocturia	moderately differentiated	T_3N_0M	TURP
17	62	1	none	well differentiated	$T_2N_0M_0$	TURP
18	70	2	dysuria, pollakyuria, nocturia	poorly differentiated	$T_3N_0M_0$	TURP
19	59	3	none	poorly differential	$T_3N_0M_0$	none
20	63	1	none	moderately differentiated	$T_1N_0M_0$	TURP

1. symptoms and signs during the 3 weeks before the inclusion
2. staging according to the TNM system (T = tumor, N = node, M = metastasis)

Results

The demographic characteristics of the patients are shown in Table 1. The mean age (68.8; range: 56–83), extent of urinary symptoms, stages of prostatic disease were comparable in both groups. No patient dropped out during the course of the study and all completed entirely the 3-month study period.

Testosterone concentrations: After the injection of triptorelin, testosterone levels increased rapidly to a mean peak concentration (C_{max}) of 35.00 nmol/l and 36.00 nmol/l for DLGSD-3-95-21 and DLGSD-3-95-22, respectively, achieved 2 days after dosing with both formulations. Thereafter, the testosterone concentrations decreased rapidly during the following 2 to 3 weeks and reached castration levels (T_{cast} = 1.735 nmol/l) within 3 to 4 weeks post-injection except for one patient of each group (Table 2). Mean testosterone levels remained below T_{cast} for the next 2 months as shown in Figure 1.

Triptorelin concentrations: After the injection, triptorelin levels increased rapidly in plasma and reached a mean peak concentration (C_{max}) of 74′343 pg/ml at 4 hours (T_{max}) for formulation DLGSD-3-95-21, and 58′968 pg/ml at 6 hours for formulation DLGSD-3-95-22. During the following 2 weeks triptorelin concentrations decreased progressively and

Table 2. Testosterone plasma levels: mean (± SD) pharmacodynamic parameters

Formulation	**DLGSD-3-95-21**	**DLGSD-3-95-22**
C_{max} (pg/ml)	35.00	36.00
(SD)	(11.17)	(10.81)
T_{max} [median] (d)	2	2
(range)	(0.17–2)	(1–7)
C_{min} (nmol/l)	0.63	0.74
(SD)	(0.31)	(0.28)
T_{min} [median] (d)	60	63
(range)	(35–84)	(35–84)
T_{cast} [median] (d)	21	28
(range)	(14–28)	(21–42)
$AUC_{0-84days}$ (day.nmol/l)	311	369
(SD)	(70)	(98)
Number of patients Castrated by day 28	9	9

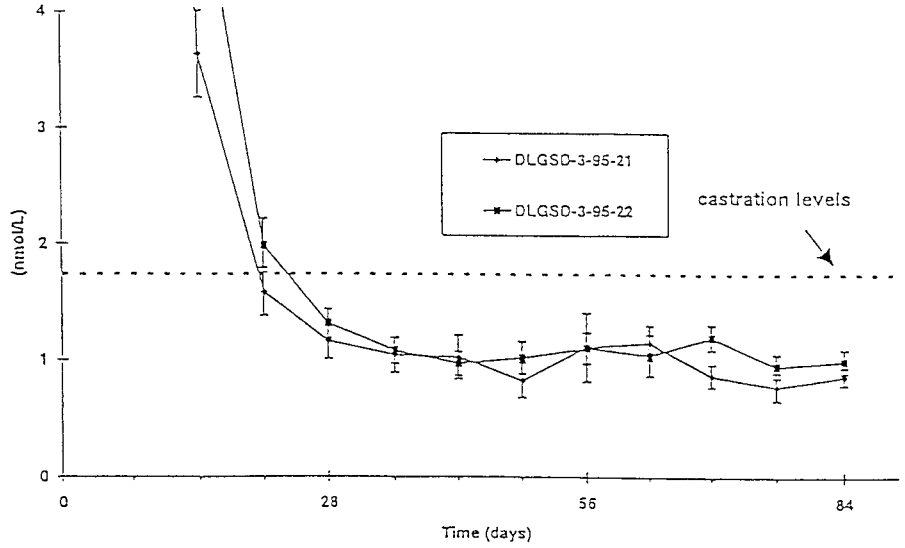

Figure 1. Plasma: focus on mean (+ sem – n = 10) testosterone levels versus time plot.

Table 3. Triptorelin plasma levels: mean (± SD) pharmacokinetic parameters

Formulation	**DLSGD-3-95-21**	**DLGSD-3-95-22**
C_{max} (pg/ml)	74′343	58′968
(SD)	(24′946)	(23′430)
T_{max} [median] (h)	4	6
(range)	(4–10)	(2–8)
$AUC_{0-8days}$ (day.pg/ml)	96′484	81′729
(SD)	(25′476)	(26′620)

then during the last 2 to 4 weeks with both formulations (Table 3).

Bone pain: On day 0 and before injection of triptorelin, bone pain was present in 2 patients, the intensity being moderate (VAS: 33 and 51, respectively). Analgesics were given (paracetamol 750 mg PO per day for one patient, and tilidin 112.5 mg PO per day for the other), and relief of pain was observed for both patients on day 28. Another patient complained of moderate pain between days 21 and 56 (VAS: 28 and 22) which was relieved with tilidin (112.5 mg PO per day).

Dysuria: On day 84, an improvement of dysuria compared to baseline was observed in one patient while micturition difficulties remained stable in the other patients.

Status performance: When analyzing the performance status scale, an overall improvement was noted in 6 patients while there was no change in performance status noted in the remaining patients. In no patient was any worsening of status observed.

Local tolerance and side effects: In all patients, the local tolerance at injection site was excellent. No local pain, induration or infection, redness, bruising or swelling were observed. Mild adverse events consisting of hot flushes were noted in 2 patients. These adverse events were transient and disappeared within a few weeks without treatment. There was no flare up due to transient rise in testosterone at the beginning of the study. No patient experienced pain or an increase of previous bone pain during the first days following triptorelin administration, but one patient exhibited increased bone pain 3 weeks after the injection. No patient complained of decreased libido or impotence, but most of cases were not sexually active either before or after starting triptorelin.

Biological parameters: There were no changes of laboratory parameters during the 3-month study period except for 2 patients. In one patient, slow hemoglobin levels were recorded in relation with a paraneoplastic anemia or an anemia due to chronic disease. In another patient, leucocytosis was noted on day 84, probably reflecting an inflammatory response to the cancer.

Discussion

Most patients with prostatic carcinoma respond to androgen deprivation, and hormonal therapy is

considered as the mainstay of treatment of disseminated prostatic carcinoma. Based on the results of this study, it is concluded that this new sustained release triptorelin pamoate is able of inducing, in patients suffering from prostatic carcinoma, pharmacological castration within 28 days and of maintaining this castration till day 84. Both formulations of triptorelin pamoate resulted in comparable testosterone pharmacodynamics. However, formulation DLGSD-3-95-21 showed a tendency to castrate patients more rapidly than formulation DLGSD-3-95-22 (median T_{cast} 21 days versus 28 days). While the total exposure to testosterone, as expressed by the mean testosterone $AUC^{1}_{0-84days}$, tended to be smaller (311 d.nmol/l) with DLGSD-3-95-21 as compared to DLGSD-3-95-22 (369 d.nmol/l), the maintenance of castration was similar for both formulations, but during the last 3 weeks of study period testosterone levels tended to be higher with DLGSD-3-95-22 while still in castration range. Concerning triptorelin pharmacokinetics, it should be noted that the bioavailability of formulation DLGSD-3-95-21 tended to be greater than that of formulation DLGSD-3-95-22. This may explain the quicker onset of castration with formulation DLGSD-3-95-21 and its slighter better maintenance of low testosterone levels during the 3rd month.

A major advantage of GnRH analogues is that they avoid the trauma of orchiectomy as well as the side effects of estrogen therapy (e.g. platelet adhesiveness). In term of clinical end-points, both formulations were similar and the local tolerance was excellent in all cases. No adverse event was recorded except transient hot flushes in two patients and slight bone pain in one; there was no clinical flare-up of the disease due to the transient rise in testosterone at the beginning of the study.

In conclusion, our data indicate that both formulations of sustained release triptorelin pamoate 11.25 mg are safe and effective in inducing pharmacological castration in patients suffering from prostatic carcinoma. In view of the findings of this study, it is concluded that DLGSD-3-95-21 is the formulation of choice to be used for clinical treatments and further investigation. This new triptorelin 3-month controlled release formulation given represents a convenient administration form and an alternative therapeutic modality for patients with prostatic carcinoma, avoiding injections every month.

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