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Leuprorelin
A Review of its Pharmacology and Therapeutic Use in Prostatic Disorders

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Summary

Synopsis

Leuprorelin (leuprolide acetate) is a synthetic analogue of gonadotrophin-releasing hormone (GnRH) [luteinising hormone–releasing hormone (LHRH)] which initially stimulates luteinising hormone (LH) and hence testicular androgen release; continuous administration then results in profound suppression of these hormones. Testosterone levels associated with castration are attained within 3 to 4 weeks. A biodegradable subcutaneous or intramuscular depot formulation of leuprorelin 3.75 or 7.5mg, which releases the drug at a constant rate over 28 days, is available and may be preferred over daily subcutaneous injections.

The progression of previously untreated advanced prostatic cancer is delayed in 70 to 90% of men receiving leuprorelin, with median survival of approximately 2 years. The efficacy of leuprorelin is equivalent to that of estrogen therapy, but the tolerability of the GnRH analogue is far better. In contrast to most other studies of GnRH agonists, a slight survival advantage has been reported for combined treatment with leuprorelin and the antiandrogen flutamide. Small noncomparative trials reveal that leuprorelin also causes regression of benign hyperplastic prostate tissue with corresponding relief of obstructive, but not irritative, symptoms although continuous treatment is necessary to maintain remission.

Impotence and flushing occur in most leuprorelin recipients but, unlike diethylstilbestrol (stilboestrol), cardiovascular toxicity and gynaecomastia are not significant problems. Symptom flare, usually manifested as bone pain in prostate cancer patients and exacerbation of obstructive symptoms in those with benign prostatic hypertrophy, can occur in 4 to 29% at the beginning of treatment.

Leuprorelin treatment is therefore an established effective palliative measure in men with previously untreated advanced prostatic cancer, and may have a role in those with benign hypertrophy who are unfit for surgery.

Pharmacodynamic Properties

Leuprorelin (leuprolide acetate) is a synthetic agonist analogue of gonadotrophin-releasing hormone (GnRH) [luteinising hormone–releasing hormone (LHRH)] with up to 80 to 100 times the potency of the native hormone. Administration is initially associated with stimulation of pituitary release of luteinising hormone (LH), causing an increase in testicular androgen production. Continued administration results in 'down-regulation' and desensitisation of pituitary GnRH receptors, and is associated with a decline in LH release and suppression of gonadal androgen synthesis.

Peak serum LH levels occur within 4 days of beginning subcutaneous leuprorelin administration in men with prostate cancer and healthy male volunteers, and usually decline thereafter with further treatment, reaching levels significantly below baseline after 2 weeks and which remain suppressed with continuous therapy. The biological activity of LH is also reduced. Although follicle-stimulating hormone (FSH) levels reach a minimum within 1 month, levels may increase again, but are still lower than pretreatment values.

The profile of LH release dictates testosterone synthesis in the testes. Therefore, serum testosterone levels reach a peak peak within 2 to 4 days of initiating leuprorelin treatment and then rapidly fall to reach levels associated with castration (< 1.7 nmol/L) within 3 to 4 weeks. This suppression has been shown to persist for up to 7 years in men with prostate cancer. Serum levels of the pharmacologically active androgen, dihydrotestosterone, parallel those of testosterone, and intratesticular and intratubular levels are profoundly depressed.

Leuprorelin inhibited growth of androgen-dependent Dunning R3327 prostate adenocarcinoma *in vivo* but not *in vitro*, suggesting an antitumour activity mediated through its effect on androgens rather than a significant direct action.

Pharmacokinetic Properties

Since it is a peptide, leuprorelin is orally inactive and thus is generally given subcutaneously or intramuscularly, although other routes are being investigated. A sustained release subcutaneous or intramuscular depot formulation, in which leuprorelin is encapsulated in biodegradable poly(*d,l*-

lactide-co-glycolide) microspheres, has been developed to supersede daily injections. The drug is released from this formulation at a constant daily rate of 2.8% of the dose over 28 days.

Mean peak plasma leuprorelin concentrations of 13.1 and 47.4 μg/L occurred within 3 hours of depot subcutaneous administration of 3.75 and 7.5mg, respectively, compared with 32 to 35 μg/L 36 to 60 minutes after a subcutaneous injection of 1mg. Sustained drug release from the microspheres maintained plasma concentrations between 0.3 and 1.1 μg/L over 28 days after single 3.75 or 7.5mg depot injections. Mean concentrations ranged between approximately 0.4 to 0.6 μg/L during monthly administration of the depot formulation for up to 6 months.

Mean volume of distribution of leuprorelin 1mg was 37.1L after a single subcutaneous injection, and 36 and 33.5L following depot administration of 3.75 and 7.5mg, respectively. Total body clearance was 9.1 L/h, and elimination half-life 3.6 hours after subcutaneous 1mg injection, while corresponding values after intravenous 1mg injections were 8.3 L/h and 2.9 hours, respectively.

Therapeutic Use

Disease progression is delayed in approximately 70 to 90% (mean 87.5%) of men with previously untreated advanced prostate cancer by daily subcutaneous injection of leuprorelin 1 or 10mg, or monthly depot subcutaneous (or intramuscular) administration of 3.75 or 7.5mg depot. Partial responses or disease stabilisation usually each occur in about 43% of patients, and complete responses are rare. Median response duration is between 10 and 18 months, and median survival about 2 years. Bone pain is alleviated in a mean of 64.5% of symptomatic patients, and urinary symptoms in 80%; performance status improves in 42 to 81% of men. The efficacy of leuprorelin treatment in previously untreated men is comparable to that of diethylstilbestrol (stilboestrol) 1mg 3 times daily or fosfestrol (diethylstilbestrol diphosphate) 100mg 3 times daily, but the GnRH agonist has a significantly better tolerability profile.

A large, well-controlled study has demonstrated that daily subcutaneous leuprorelin plus oral treatment with the antiandrogen flutamide 250mg 3 times daily extends median progression-free survival by nearly 3 months, and median overall survival by over 7 months, representing small but significant increases. Survival advantage of combination therapy was particularly striking in a small subgroup of patients with good performance status and minimal metastatic bone involvement. However, studies combining other GnRH agonists with flutamide fail to demonstrate increased survival versus GnRH agonist alone and therefore the encouraging results obtained with leuprorelin plus flutamide require further confirmation.

In small numbers of men with benign prostatic hypertrophy, subcutaneous leuprorelin 1 mg/day reduced prostate size by 45% within 6 months, accompanied by relief of obstructive symptoms and minimal alleviation of irritative symptoms. Continuous leuprorelin treatment is necessary to maintain clinical remission, and should perhaps therefore be reserved for those patients in whom prostatectomy would present an unjustifiable risk of morbidity.

Tolerability

The adverse effects of leuprorelin are largely a result of alterations in sex hormone levels during treatment.

The initial stimulation of testosterone production which occurs in the first few days of leuprorelin treatment is associated with symptom flare in 4 to 29% of patients – usually bone pain, paraesthesiae, spinal cord compression, and dysuria from ureteric compression in patients with prostate cancer; a worsening of obstructive symptoms may occur in those with benign hyperplasia. Concomitant antiandrogen or diethylstilbestrol treatment during the first 2 weeks of leuprorelin administration reduces symptom flare.

Impotence and decreased libido are universal and hot flushes, usually mild and tolerable, occur in 35 to 71% during long term leuprorelin therapy. In contrast to estrogens, cardiovascular side effects (e.g. peripheral oedema, thrombosis, embolism, myocardial ischaemia) and gynaecomastia are rarely associated with leuprorelin. Mild nausea, diarrhoea and vomiting occur in 5 to 14% of leuprorelin recipients and local reactions (pain, fibrosis, pruritus) have been reported in 2 to 3% of men receiving the subcutaneous depot formulation.

Dosage and Administration

In men with advanced prostate cancer or benign prostastic hypertrophy, leuprorelin 3.75 or 7.5mg is administered as a subcutaneous or intramuscular biodegradable sustained release depot once every 4 weeks. The injection site should be reviewed periodically. This method of administration is superseding daily subcutaneous injections of 1mg. Caution should be exercised or other means of androgen ablation should be considered in men with prostate cancer at risk from spinal cord compression or ureteric obstruction due to symptom flare during the first 2 weeks of treatment. This may be avoided by giving concomitant antiandrogen or diethylstilbestrol 1mg 3 times daily for 1 week before and 1 week after the first leuprorelin dose.

Under normal circumstances, the hypothalamus releases pulses of gonadotrophin-releasing hormone (GnRH) [luteinising hormone–releasing hormone (LHRH); or gonadorelin] which in turn stimulates the anterior pituitary gland to release the gonadotrophins luteinising hormone (LH) and follicle-stimulating hormone (FSH) about every 90 minutes. In males, LH causes the testicular Leydig cells to synthesise testosterone which, in the presence of FSH, promotes spermatogenesis. Testosterone regulates pituitary release of LH and FSH via a negative feedback system, and this governs GnRH production (Eisenberger et al. 1986; Glode 1986; Swanson et al. 1988).

The pulsatile nature of GnRH release is imperative for this normal physiological function as the

study after 6 months' daily leuprorelin treatment (Vance & Smith 1984), and in 5 of 20 others given a single subcutaneous depot injection of 3.75, 7.5 or 15mg (Mazzei et al. 1989). Serum testosterone levels were nevertheless suppressed to castrate levels (< 2 nmol/L) in all patients, suggesting that although a reduction in LH could not be detected using immunoreactive assays, the biological activity of LH was inhibited. Indeed, serum levels of biologically active LH were decreased by 98% in 19 men with previously untreated prostate cancer, being undetectable (< 0.4 U/L) in 17 (Santen & Warner 1985; Warner et al. 1983). Leuprorelin 1 mg/day subcutaneously also decreased bioactive LH serum levels significantly in 26 women undergoing controlled ovarian hyperstimulation (Cedars et al. 1990), and other GnRH agonists have been reported to alter the activity of LH (see reviews by Chrisp & Goa 1990, 1991).

The profile of FSH suppression during leuprorelin treatment differs from that of LH. Following the initial stimulation, serum FSH levels reached a nadir of 3 to 7 U/L within 2 to 4 weeks of beginning therapy with leuprorelin 1 or 10 mg/day subcutaneously, or 3.75 or 7.5 mg/month depot injection in men with previously untreated or treated prostate cancer (Bischoff et al. 1990; Glode et al. 1987; Santen et al. 1984; Smith 1984a; Vance & Smith 1984) and in men with benign prostatic hypertrophy (Gabrilove et al. 1989). The decline in serum FSH was more rapid than the decrease in LH levels (Mazzei et al. 1989). Levels then steadily increased (fig. 2) to plateau between 10 and 15 U/L after 4 to 6 months; this persisted for 1 to 3 years. Despite the elevation compared with the maximum decrease, FSH levels remained below baseline values. In 3 of 20 patients receiving a single subcutaneous leuprorelin 3.75 or 7.5mg depot injection, serum FSH levels were not significantly suppressed after 5 weeks (Mazzei et al. 1989).

1.2 Effect on Androgens

A depot injection of leuprorelin 3 mg/kg to male rats caused a rapid increase in serum testosterone, followed by a profound suppression maintained for over 6 weeks (Ogawa et al. 1989). Mean serum testosterone levels in male rats were significantly reduced after 14 to 28 days' subcutaneous administration of leuprorelin 0.2 to 1.8μg daily, resulting in inhibition of spermatogenesis and reduction in prostate, testes and seminal vesicle weight (Heber et al. 1984; Kim et al. 1988; Labrie et al. 1980; Rajfer et al. 1984a). Leuprorelin 14 μg/kg significantly decreased nuclear, but not cytoplasmic, androgen receptor concentration in male rats (Rennie et al. 1988).

In 38 and 41 men with prostatic cancer, 8 hours after subcutaneous injection of leuprorelin 1 or 10mg mean serum testosterone level increased from 11 nmol/L to a peak of 13 to 16 nmol/L (Santen & Warner 1985; Warner et al. 1983). Testosterone levels continue to increase with further daily administration, or injection of leuprorelin 3.75 or 7.5mg depot, to maxima of between 14 and 23 nmol/L (50 to 100% of baseline values), achieved 2 to 4 days after beginning treatment (Leuprolide Study Group 1984; Mazzei et al. 1989; Santen & Warner 1985; Sharifi et al. 1990; Smith 1984a; Smith et al. 1985). A rapid decline in serum testosterone levels then occurs, to 3 to 4 nmol/L within 2 weeks (Mazzei et al. 1989; Santen & Warner 1985; Smith 1984a; Smith et al. 1985). Castrate levels (< 1.7 nmol/L) are obtained after 3 to 4 weeks of leuprorelin therapy (Bischoff et al. 1990; Glode et al. 1987; Leuprolide Study Group 1984; Mazzei et al. 1989; O'Brien & Hibberd 1990; Santen & Warner 1985; Sharifi et al. 1990), representing a decrease of at least 94% compared with pretreatment values (Santen & Warner 1985).

The mean time to reach castration testosterone levels after subcutaneous or intramuscular injections of leuprorelin 3.75 or 7.5mg depot was 21 to 23 days (Akaza et al. 1990; Sharifi et al. 1990). Testosterone synthesis remained in this range during up to 7 years' leuprorelin therapy (fig. 3) [Glode et al. 1987; Isurugi et al. 1989; O'Brien & Hibberd 1990; Santen et al. 1984; Smith 1984b; Smith et al. 1985; unpublished data on file, TAP Pharmaceuticals and Takeda Chemical Industries]; no 'acute-on-chronic' effect on testosterone release was noted after 1 year's treatment (Glode et al. 1987). Indi-

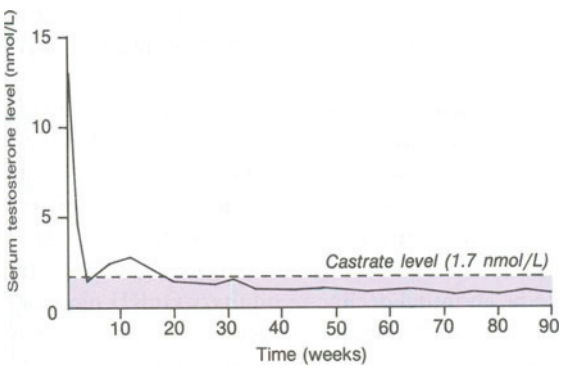

Fig. 3. Mean serum testosterone levels in 48 men with prostatic cancer during 4-weekly treatment with leuprorelin 3.75 or 7.5mg depot subcutaneously (adapted from O'Brien & Hibberd 1990).

vidual transient elevations in serum testosterone level have been reported, but these were ascribed to incorrect leuprorelin depot injection technique at the beginning of treatment (fig. 3) [O'Brien & Hibberd 1990]. Similarly, 4 of 53 patients in 1 study had 1 serum testosterone value above the castrate limit, but these were isolated incidents since no 2 consecutive levels above 1.7 nmol/L were observed during 6 months' depot treatment (Sharifi et al. 1990). Prolonging the interval between intramuscular depot injections of leuprorelin 7.5mg from 4 to 5 weeks resulted in a transient elevation in serum testosterone in 1 of 5 patients (Sharifi et al. 1990). The injection could be delayed by up to 12 days beyond the recommended 28 with no clinically significant increase in testosterone levels.

Since it is produced by the action of 5α-reductase on testosterone, serum dihydrotestosterone levels parallel those of testosterone during leuprorelin therapy. Serum levels of dihydrotestosterone increased from 1 to 2 nmol/L to a peak of 2 to 4 nmol/L after 2 to 4 days, and declined thereafter to approximately 0.2 to 0.7 nmol/L within a month in men with prostate cancer (Bischoff et al. 1990; Mazzei et al. 1989; Santen et al. 1984; Smith 1984a; Smith et al. 1985; Warner et al. 1983) and in men with benign prostatic hypertrophy (Gábrilove et al. 1989).

Serum levels of 17α-hydroxyprogesterone and androstenedione, produced both in the testes and adrenal cortex, tended to increase in the first 8 to 72 hours of daily treatment with leuprorelin 1 or 10mg, and then decreased by approximately 60 to 80% after 4 to 7 weeks (Warner et al. 1983).

Tissue androgen levels were also decreased. In 15 men with prostate cancer receiving leuprorelin depot (n = 6), goserelin (6) or buserelin (3), mean intratesticular levels of testosterone decreased from 335 to 4.6 ng/g tissue weight and dihydrotestosterone decreased from 25.3 to 3.7 ng/g; intratubular levels of testosterone were reduced from 50.8 to 0.1 ng/g, and dihydrotestosterone from 7.5 to 0.6 ng/g (Nagai et al. 1989). There was also a decrease from 15.3 to 0.4 pg/mg tissue weight in mean crude nuclear dihydrotestosterone level.

The long term suppression of androgen synthesis by leuprorelin results also in Leydig cell hypoplasia and inactivity, aspermatogenesis and increased seminiferous tubule membrane thickness in men (of mean age 62 to 74 years) with prostate cancer (Nagai et al. 1989; Rajfer et al. 1984b; Smith & Urry 1985).

1.3 Antitumour Activity

The effect of subcutaneous leuprorelin administration on the growth of implanted poorly- or well-differentiated androgen-dependent Dunning R3327 prostate adenocarcinoma in rats has been investigated. The mean time taken for tumour volume to double increased significantly from 1.7 to 1.95 days after administration of leuprorelin 1000 μg/kg 5 days each week for 20 days, and to 2.4 days in surgically castrated animals (Pollack et al. 1984). Tumour weight was reduced by 33% in animals given leuprorelin 1000 μg/kg and by 85% in the castrate group compared with untreated animals. Leuprorelin 1 or 50 μg/kg for 5 days each week had no significant effect on tumour growth, despite apparently producing a similar suppression of serum testosterone levels as daily administration (Pollack et al. 1984). However, there was a delay in testosterone synthesis inhibition with the 5-days-per-week schedule.

Administration of leuprorelin 333 or 1000 μg/

kg once daily, or 333 μg/kg in 2 divided daily doses decreased mean tumour weight by 35%, 50% and 67%, respectively, after 2 months in rats (Ichikawa et al. 1988). However, only monthly administration of sustained release leuprorelin 333 μg/kg/day induced a slowing of tumour growth and reduction in tumour weight (87%) comparable to that achieved in castrated animals (95%). Maintenance of steady-state plasma leuprorelin concentrations, and hence testosterone depression, was more consistent in animals given the sustained release formulation (see also section 2.1).

Combined daily treatment with leuprorelin 25μg subcutaneously plus the antiandrogen flutamide 15 mg/kg orally for 4 weeks reduced tumour growth (*vs* controls) by 76%, compared with 44% in animals given leuprorelin alone, 89% in flutamide only–treated rats and 93% in castrated animals (Kung et al. 1988). 3 weeks after discontinuing leuprorelin or flutamide, tumour growth was similar to that in untreated animals.

The proportion of hyperdiploid tumour cells was lower in animals given leuprorelin 1000 μg/kg/day for 5 days per week and, more markedly, in castrated rats compared with controls; the fraction of cells in the mid-S phase of mitosis was reduced approximately 20 to 30% by leuprorelin 1, 50 or 1000 μg/kg and by orchidectomy (Pollack et al. 1984).

In vitro, leuprorelin 79 μmol/L (100 mg/L) had no effect on rat prostate cancer cell proliferation, suggesting a lack of direct antitumour activity (Pollack et al. 1984). Furthermore, natural killer cell activity, which may be clinically important, determined from the lysis of K-562 erythroid cells by peripheral blood mononuclear cells from 9 volunteers, 2 patients with benign prostatic hypertrophy and 1 with prostate cancer, was increased 3% (not significant) by leuprorelin 100 μmol/L, compared with an 82% reduction in the presence of diethylstilbestrol (stilboestrol) 100 μmol/L (Ablin et al. 1988).

1.4 Mechanism of Action

The therapeutic effects of leuprorelin (and other GnRH agonist analogues) in disorders of the prostate appear to be almost entirely due to its ability to induce and maintain suppression of testicular androgen synthesis via its effects on pituitary LH release.

Following an initial stimulation, serum levels of immunoreactive and biologically active LH decrease to below baseline values within 2 weeks of continuous exposure to leuprorelin as the pituitary becomes refractory to further stimulation. The mechanism involved is unclear, but there appears to be an initial decline in pituitary GnRH receptor population, followed by a return to normal levels but accompanied by an uncoupling of the receptors from intracellular effector processes (Conn & Crowley 1991). As a consequence of the inhibition of LH secretion and activity, testicular testosterone synthesis (and therefore dihydrotestosterone) is also inhibited, reaching serum levels associated with orchidectomy within a month of commencement of leuprorelin therapy. These levels are maintained by subcutaneous or intramuscular injection of leuprorelin 3.75 or 7.5mg depot every 4 weeks, or by daily subcutaneous injections of 1 or 10mg.

Between 70 and 80% of prostatic carcinomas and all benign prostatic hyperplasia appears to depend on androgens to proliferate (Brendler 1990; Catalona & Scott 1978; Korman 1989; Wojciechowski et al. 1986). Tumour and tissue development should therefore be slowed by the decrease in circulating testosterone and its metabolite dihydrotestosterone, the active androgen which promotes cell growth through binding to cytoplasmic and nuclear androgen receptors (Eisenberger et al. 1986; Korman 1989).

In vivo studies reveal leuprorelin activity against androgen-sensitive tumours which appears to be related to suppression of serum testosterone levels. A direct effect is unlikely, since leuprorelin did not inhibit prostate tumour cells *in vitro* (see section 1.3). Furthermore, prostatectomy samples from 12 men with prostate cancer who had received subcutaneous leuprorelin 1mg/day with (n = 3) or without (n = 9) flutamide 250mg 3 times daily generally for 3 to 4 months revealed a reduction in neoplastic gland density but no gland degeneration implying that neoplasia was supressed rather than eradicated by therapy (Murphy et al. 1991). High

affinity binding of an unspecified GnRH agonist was, however, evident in the human androgen-sensitive prostate cancer cell line LNCaP *in vitro*, and in 19 of 22 malignant and 49 of 54 benign prostatic tumours, suggesting that secondary direct activity cannot be discounted (Waxman et al. 1990).

2. Pharmacokinetic Properties

Like other GnRH agonists, leuprorelin is a peptide and therefore susceptible to the action of intestinal proteolytic enzymes. Thus, when given orally, the bioavailability of the drug is less than 1% (Shimamoto 1987; Vadnere et al. 1990). Although a variety of other routes of administration, including intranasal, pulmonary, transdermal, rectal and sublingual, have therefore been investigated (Meyer et al. 1990; Shimamoto 1987; Vadnere et al. 1990), subcutaneous and intramuscular delivery have received the most attention and have been used clinically.

Continuous administration of leuprorelin is necessary to desensitise the pituitary gland and ultimately inhibit testosterone synthesis. Therefore, to avoid an onerous schedule of daily subcutaneous injections, a sustained release depot formulation, injected subcutaneously or intramuscularly each month, has been developed to aid convenience, compliance and efficacy (Toguchi 1990).

In this depot formulation, leuprorelin is entrapped in poly(*d,l*-lactide-co-glycolide) polymer microspheres; the polymer maxtrix is completely biodegraded to lactic and glycolic acids, which are metabolised by usual processes (Toguchi 1990).

In vitro and *in vivo* studies revealed that a microsphere lactic to glycolic acid ratio of 75 : 25 and molecular weight of 14 000 yielded leuprorelin release characteristics most suitable for once monthly administration (Ogawa et al. 1988a,b).

Following administration of this dosage form there is a transient rapid release of leuprorelin (probably due to leaching from the microsphere surfaces), and then a steady almost zero-order release (i.e. at a constant rate) of drug lasting 35 days as the polymer matrix hydrolyses (Ogawa et al. 1988b). 28 days after subcutaneous or intramuscular injection of leuprorelin 0.9 to 1.35mg in microspheres to rats, approximately 10 to 20% of the original dose remained microencapsulated at the injection site (Ogawa et al. 1988a, 1989). A release rate of 2.8% of the dose per day was calculated (Okada et al. 1988).

The disposition of leuprorelin following daily subcutaneous injection and monthly depot administration has been studied in healthy volunteers and in elderly (aged over 65 years) patients with prostatic cancer. A radioimmunoassay with a detection limit of 50 ng/L was used to determine serum leuprorelin concentrations (Yamazaki & Okada 1980; Ueno & Matsuo 1991) and a high performance liquid chromatography (HPLC) system coupled to radioimmunoassay to identify leuprorelin metabolites has been described (Ueno & Matsuo 1991).

2.1 Plasma Concentrations

Following a single subcutaneous injection of leuprorelin 1mg, mean maximum plasma concentrations (C_{max}) of 32.3 to 35 μg/L were achieved within a mean of 36 to 60 minutes in 6 healthy volunteers (Sennello et al. 1986) and 3 patients with prostate cancer (Imai et al. 1986, 1987a).

Within 3 hours of subcutaneous injection of leuprorelin depot 3.75, 7.5, 15 or 30mg in 23 prostatic cancer patients, mean C_{max} values of 13.1, 47.4, 54.5 and 53.1 μg/L occurred, respectively, representing rapid absorption from the surfaces of the microspheres at the injection site (Mazzei et al. 1989). During this phase, which lasted 1.2 to 2 hours, the corresponding rates of drug release from the depot formulation were estimated to be 583.4, 2031.9, 2608.5 and 2658.8 μg/h, respectively. Mean leuprorelin concentrations declined following this initial peak, to reach 1.6 and 2.7 μg/L 24 hours after administration of the 3.75 and 7.5mg depots, respectively. Averaged over the course of the first day of 3.75 or 7.5mg depot subcutaneous or intramuscular injection, plasma leuprorelin concentrations ranged between 1.2 and 2 μg/L (Niijima et al. 1990; Sharifi et al. 1990). The values of the area under the plasma concentration-time curves ($AUC_{0-\infty}$) were comparable following subcutan-

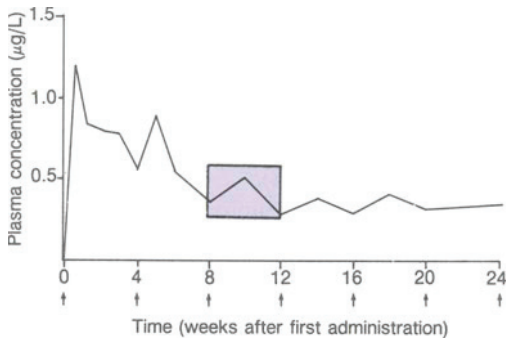

Fig. 4. Mean plasma leuprorelin concentrations in 56 men with prostatic cancer following monthly intramuscular administration of leuprorelin 7.5mg depot (indicated by arrows) [adapted from Sharifi et al. 1990]. The shaded area highlights the biphasic monthly concentration profile.

eous and intravenous 1mg injections in 6 volunteers (118.6 and 125.8 μg/L • h). Depot injection of leuprorelin 3.75, 7.5 and 15mg resulted in respective apparently dose-related $AUC_{0\text{-}35d}$ values of 541.7, 990.5 and 1323.9 μg/L • h in 22 prostate cancer patients (Mazzei et al. 1989).

The sustained release phase maintained plasma leuprorelin concentrations between 0.3 and 1.1 μg/L for 28 days after a single 3.75 or 7.5mg injection (Mazzei et al. 1989l; Niijima et al. 1990). The release rates during this phase were 2.9 μg/h for the 3.75mg formulation, and 4.3 to 4.6 μg/h for the 7.5μg dosage. Plasma leuprorelin concentrations remained steady at approximately 0.4 to 0.6 μg/L with continued monthly subcutaneous or intramuscular depot injection for 12 or 24 weeks in 2 groups of 29 and 56 patients (fig. 4) [Niijima et al. 1990; Sharifi et al. 1990]. There was a peak in mean plasma concentration about 14 days after each depot administration which divided each 4-weekly profile into 2 phases (fig. 4), reflecting apparent zero-order release of drug from the disintegrating polymer depot (Mazzei et al. 1989).

A developmental nonbiodegradable vinyl polymer composite containing leuprorelin 100 to 250mg resulted in detectable plasma drug concentrations for over 3 months in 11 patients, with therapeutic concentrations maintained in 1 patient for over 88 weeks (Imai et al. 1987a,b).

2.2 Distribution

Distribution varied considerably between individuals (Sennello et al. 1986). The mean volume of distribution at steady-state (V_{ss}) following a single subcutaneous injection of leuprorelin 1mg was 37.1L in 6 volunteers (Sennello et al. 1986), and 36, 33.5 and 27.4L after depot administration of 3.75, 7.5 and 15mg, respectively, in 22 prostatic cancer patients (Mazzei et al. 1989).

V_{ss} was similar (26.5L) following an intravenous bolus of leuprorelin 1mg, despite a significant difference between the apparent volume of distribution of the central compartment (in a 2-compartment model) [V_c] obtained with subcutaneous versus intravenous administration (25.1 *vs* 9.2L) [Sennello et al. 1986].

The peripheral compartment therefore must have compensated to give the similar values for V_{ss}. The distribution volumes for leuprorelin may reflect the relatively hydrophilic nature of the drug (Sennello et al. 1986).

2.3 Elimination

2.3.1 Metabolism

In animals, leuprorelin was metabolised to the (5-9) pentapeptide, (5-7) tripeptide, (1-3) tripeptide and (1-2) dipeptide (Ueno & Matsuo 1991). The (5-9) pentapeptide would be expected to be the major metabolite, since this is the main species of degradation of buserelin, another nonapeptide ethylamide analogue of GnRH (Brogden et al. 1990), and the metabolism of goserelin and nafarelin, other GnRH analogues, principally yields the corresponding (5-10) hexapeptides (Chrisp & Goa 1990, 1991). These metabolites are formed by cleavage of the Ser^4-Tyr^5 bond, a process which occurs with endogenous GnRH in the kidney (Stetler-Stevenson et al. 1981). Further peptidase activity could then result in smaller peptide fragments (Chrisp & Goa 1990, 1991).

Within 1 hour of intramuscular injection of leuprorelin 3.75mg depot to a patient with prostatic cancer, a serum (5-9) pentapeptide concentration of 150 ng/L was detected, increasing to a maxi-

mum of 860 ng/L after 3 hours (Ueno & Matsuo 1991). In a second leuprorelin recipient, the concentration of this metabolite in the urine reached a peak of 4.97 μg/L within 2 days, and could still be detected (1.74 μg/L) after 29 days (Ueno & Matsuo 1991).

2.3.2 Excretion

Since other GnRH agonists are mainly excreted in the urine (Brogden et al. 1990; Chrisp & Goa 1990, 1991) this would be similarly expected with leuprorelin, although published data confirming this do not appear to be available.

The mean total body clearance of leuprorelin from the plasma was similar following single subcutaneous (9.1 L/h) or intravenous (8.3 L/h) injections of 1mg in 6 volunteers (Sennello et al. 1986).

Mean elimination half-life ($t_{1/2\beta}$) was reported to be 3.6 hours after subcutaneous injection of leuprorelin 1mg, and 2.9 hours after intravenous bolus of the same dose (Sennello et al. 1986). The slower elimination of leuprorelin compared with native GnRH [$t_{1/2\beta}$ approximately 30 minutes (Jeffcoate et al. 1974)] demonstrates the increased resistance to peptidase activity conferred by structural changes.

3. Therapeutic Use in Prostatic Disorders

Older men are prone to 2 common disorders of the prostate, prostatic carcinoma and benign prostatic hypertrophy.

Prostate cancer is rare (< 1% incidence) in men aged under 50 years, but thereafter the postmortem incidence increases to an estimated 55% in men aged 60 to 80 years or 80% in those aged 65 years or over (Baum & Brown 1990; Brendler 1990; Korman 1989; Rasmussen, personal communication). It has been estimated that in the US between 60 000 and 100 000 or more new cases are diagnosed annually, and there are between 26 000 and 30 000 deaths, a cancer mortality rate which is only exceeded by lung and colorectal neoplasia in men aged over 55 years (Baum & Brown 1990; Brendler 1990; Huben & Perrapato 1991; Swanson et al. 1988; Wojciechowski et al. 1986).

Men younger than 45 years of age rarely develop benign hyperplasia of the prostate, but advancing age is associated with a sharp increase in incidence, reaching approximately 90% in men aged 80 years (Atala & Amin 1991; Brendler 1990; Sagalowsky & Wilson 1987). It is the most common cause of urethral obstructive symptoms, which usually develop at age 50 years and then gradually progress in severity and prevalence. Benign prostatic hypertrophy does not appear to be predictive of cancer development (Brendler 1990; Korman 1989).

All normal and 70 to 80% of malignant prostatic growth is dependent on circulating androgens, specifically testosterone (Brendler 1990; Catalona & Scott 1978; Korman 1989; Sagalowsky & Wilson 1987). Prostatic carcinoma and benign prostatic hypertrophy are therefore amenable to management with leuprorelin.

The use of leuprorelin in the management of prostatic cancer has been well studied both alone and in combination with antiandrogens, and has been compared with estrogen treatment. Comparisons with orchidectomy are presently lacking. There are fewer published investigations in men with benign prostatic hyperplasia, which like the earlier studies evaluating leuprorelin in prostatic cancer, used a once-daily subcutaneous injection regimen. More recently, results have been obtained following monthly subcutaneous or intramuscular administration of a sustained release depot formulation of leuprorelin in prostate cancer.

3.1 Treatment of Prostatic Cancer

Patients enrolled in clinical trials evaluating the efficacy of leuprorelin in prostate cancer had previously untreated histologically confirmed metastatic [stage D_1 (pelvic metastases) or stage D_2 (distant metastases)] or locally advanced [stage C (non-metastatic, but extending beyond the prostate)] disease, unless stated otherwise.

Objective response criteria of the United States National Prostatic Cancer Project (NPCP), the Japanese Prostatic Cancer Study Group (JPG) or the European Organisation for Research on Treatment

of Cancer (EORTC) were employed in these studies. Performance status, urinary outlet obstruction, bone pain and analgesic requirements were variously used to assess subjective response.

3.1.1 Noncomparative Studies

Disease progression was prevented in over 72% of men with previously untreated prostatic cancer given leuprorelin 1, 10 or rarely 20 mg/day subcutaneously, and in 82 to 89% of those receiving subcutaneous or intramuscular depots of 3.75, 7.5 or occasionally 15mg every 28 days (table I).

The mean proportion of patients achieving objective responses or disease stabilisation was 87.5%. Complete responses were rare, occurring only in isolated patients. The rates of partial response and no further change were very similar, about 43% (range 21 to 67%) and 42% (range 27 to 64%), respectively. There were no significant differences between the responses to leuprorelin 1 or 10mg daily (Smith et al. 1985; Vance & Smith 1984), or to 3.75 or 7.5mg depot each month (Niijima et al. 1990; O'Brien & Hibberd 1990; Rizzo et al. 1990).

Using JPG criteria Niijima et al. (1990) reported complete or partial response rates, and disease stabilisation (no change) in 1, 55 and 30%, respectively, compared with corresponding rates of 1, 21 and 64% using the more stringent NPCP recommendations. Persistent elevated serum acid phosphatase levels, despite a decrease in tumour size, would be graded as stable disease rather than partial response using the latter guidelines (see Korman 1989).

The median duration of response varied between 10 and 18 months in previously untreated patients, and median survival was 22.5 to 25 months.

Objective response did not appear to be significantly related to disease severity. Although disease progression occurred only in 1 of 12 and 5 of 41 patients with stage D disease in 2 studies, and not in the remaining men with disease of stage B (n = 7) or C (n = 2), complete responses were also induced in 2 men with the most severe disease (Rizzo et al. 1990; Yamanaka et al. 1985). Patients with evaluable bone metastases responded better than those with localised disease in 1 study; complete responses occurred in 16 (42%) versus 2 of 38 (5%), partial responses in 9 (24%) versus 4 (11%) and stabilisation in 10 (26%) versus 31 (82%) [Rizzo et al. 1990]. Conversely, Akaza et al. (1990) reported 3 partial responses in 42 patients with bone metastases (7%), compared with 48 in 89 men with primarily prostatic involvement (54%), and 2 partial and 3 complete responses in 11 others with soft tissue metastases (45%). Of the group with bone lesions, 32 (76%) had no change in their disease. The differences in reported sensitivity of disease sites to leuprorelin may reflect the difficulty in assessing pelvic lymph node and bone responses compared with soft tissue (Korman 1989).

Elevated serum prostatic acid phosphatase levels decreased by at least 25% in 29 of 32 patients (91%) after 3 monthly depot injections of leuprorelin 7.5mg, and in 20 of 26 (77%) after 6 months (Sharifi et al. 1990). Levels returned to normal, therefore satisfying 1 of the NPCP criteria for objective response, within 4 months in 26 of 51 other patients (51%), and decreased by over 50% in 22 (43%) [Akaza et al. 1990]. Minimum prostatic acid phosphatase serum levels were attained in the third month of depot therapy (Rizzo et al. 1990).

Subjectively, leuprorelin alleviated bone pain in 37 to 94% (mean 64.5%) of affected patients and relieved urinary symptoms in 73 to 88% (mean 80%). Eastern Cooperative Oncology Group (ECOG) or WHO performance status improved in between 42 and 81%, with 34 of 46 men (74%) in 1 study reporting an improvement in well-being (O'Brien & Hibberd 1990).

Unlike previously untreated patients, men receiving leuprorelin after prior hormonal manipulation did not respond. There were no complete responses, 1 partial response (5%) and 9 cases of disease stabilisation (43%) in 21 previous recipients of hormone therapy, usually diethylstilbestrol; stage D_2 disease progressed in the remaining 11 patients (52%) [Smith et al. 1985]. The lack of progression in this instance was probably related to the natural history of the disease rather than to a drug effect (Smith, personal communication). Within 4 months of beginning daily leuprorelin

Table I. Some noncomparative studies of daily subcutaneous injection or monthly subcutaneous or intramuscular depot leuprorelin administration in patients with previously untreated prostatic cancer

Reference	No. of evaluable patients [mean age (years)]	Dosage (mg) [duration (months)]	Subjective response rate[a]	Objective response rate (%)[b]			Median duration of response (months)	Median survival (months)
				CR	PR	NC		
Daily subcutaneous injection								
Smith et al. (1985)	47 (NS)	1 or 10 (20)		2	38	32	≥12	
Smith (1984b)	34 (NS)	NS (≥18)			94		12 (n = 20) or 18 (n = 13)	
Trachtenberg (1983)	9 (68)	1 (3-8)	9/9		67	33		
Vance & Smith (1984)	28 (68)	1 or 10 (12)	Bone pain, 15/16; PS, 13/16	4	46	39	10	
Yamanaka et al. (1985)	19 (74)	20 (3-12)			63	32		
Monthly subcutaneous depot injection								
Bischoff et al. (1990)[c]	103 (NS)	3.75 or 7.5 (≤15)	Bone pain, 37%		33	50		25
Navratil (1990)[d]	18 (70.5)	3.75 (7)			28	56		
Niijima et al. (1990); Akaza et al. (1990)	81 (NS)	3.75 or 7.5 (3)	Bone pain, 20/31; urinary, 61/69; PS, 26/62	1	21	64		
O'Brien & Hibberd (1990)	48 (68)	3.75 or 7.5 (3-24)	PS, 18/28; urinary, 16/22; well-being, 34/46	2	60	27	16	
Rizzo et al. (1990)[e]	43 (69)	3.75, 7.5, 15 or 30 (12)	Bone pain, 10/16; urinary, 33/42	5	53	30	3.4 (0.75-10)	
Sharifi et al. (1990)	53 (68)	7.5 (6)	PS, 13/31	2	23	57		22.5

a In evaluable symptomatic patients.
b According to NPCP criteria.
c According to EORTC criteria.
d Patients also received nilutamide 100mg 3 times daily for the first 14 days of leuprorelin therapy to minimise disease 'flare'.
e 9 patients were refractory to previous hormonal therapy (estrogens, estramustine, antiandrogens).
Abbreviations: CR = complete response; PR = partial response; NC = no change, stable disease; NS = not stated; PS = performance status [Eastern Cooperative Oncology Group (ECOG) or WHO]; urinary = urinary symptoms including dysuria and/or retention.

Table II. Results of a randomised double-blind study of leuprorelin 1 mg/day subcutaneously (L) in combination with flutamide 250mg 3 times daily (F) in patients with previously untreated prostatic cancer (from Crawford et al. 1989)

No. of patients [mean age (years)]	Treatment [duration (months)]	Subjective response rate[a]	Objective response rate (%)[b]		Median survival (months)		Efficacy
			CR	PR	progression-free	overall	
303[c] (69)	L + F	PS, 27/283; bone pain, 64/280	7.9	35.7	16.5	35.6	L + F > L for survival
300[c] (68)	L (42)	PS, 22/271; bone pain, 48/272	7.1	28.2	13.9	28.3	

a Improvement in evaluable patients.
b According to NPCP criteria.
c 280 patients in the combination group and 269 in the leuprorelin monotherapy group were evaluable for objective response; all patients evaluable for survival.
Abbreviations and symbols: CR = complete response; PR = partial response; PS = ECOG performance status; > indicates significantly greater efficacy ($p < 0.05$).

therapy, 75% of the previously treated patients had progressive disease or had died. Similarly, in a group of 26 surgically castrated men, disease stabilised in 6 (23%) but progressed in the other 20 (77%) during leuprorelin treatment (Smith et al. 1985). Furthermore, 4 of the 6 patients with no initial change in disease deteriorated within 5 months.

3.1.2 Leuprorelin Combined with an Antiandrogen

The therapeutic effect of leuprorelin in prostate cancer is mediated through profound inhibition of testicular androgen synthesis (section 1.4), with no activity against adrenal androgen production, which normally represents about 5% of the total. Intraprostatic levels of the active androgen dihydrotestosterone may remain high through formation from adrenal androgens (Labrie et al. 1986). It has been proposed that castration testosterone levels and this small adrenal contribution are sufficient to stimulate proliferation of highly sensitive tumour cells and thus cause disease progression in the 15 to 30% of previously untreated patients who do not respond or relapse during GnRH agonist therapy (Crawford 1989; Labrie et al. 1986, 1987, 1988). Adding an antiandrogen such as flutamide should therefore block any stimulation produced by residual circulating androgens. Combined androgen blockade also aims to prevent the disease flare which occasionally occurs during the first 1 or 2 weeks of leuprorelin therapy due to transient elevations in serum testosterone levels (see sections 1.2 and 4).

In a large randomised double-blind trial Crawford et al. (1989) demonstrated no significant difference in the response rates of previously untreated patients with stage D_2 disease receiving daily leuprorelin with or without flutamide (table II). However, both progression-free and overall survival were slightly, but significantly, greater in combination treatment recipients. This was particularly true in men with a pretreatment ECOG performance status of 0 to 2 and minimal disease, defined as absence of rib, long bone, skull or soft tissue involvement. Although the numbers were relatively small (41 in each group), median progression-free and overall survival were 52 months each in men receiving leuprorelin and flutamide, compared with 19 and 40 months, respectively, in men receiving leuprorelin alone (fig. 5) [Crawford et al. 1990b]. Conversely, leuprorelin monotherapy recipients with poor performance status (ECOG 3) and severe disease had slightly longer progression-free (median 8.6 *vs* 8.1 months) and overall survival (median 28.3 *vs* 23.9 months) than the com

bination group, but again patient numbers were small (fig. 5).

Median overall survival was approximately 7 months shorter in 107 evaluable Black patients compared with 442 White patients (26.4 *vs* 33.3 months; p = 0.01) receiving leuprorelin alone or with flutamide (Crawford et al. 1990b). This difference was possibly associated with inherently different disease pathology and/or socioeconomic differences (e.g. worse nutritional status, delays in seeking medical attention/trial enrolment).

The results of Crawford et al. (1989, 1990b) demonstrating a small but significant survival benefit in combining leuprorelin with flutamide agree with the results obtained by Labrie et al. (1987, 1988) using the GnRH agonist (D-Trp^6 desGly^{10}) GnRH ethylamide. However, other controlled studies investigating the efficacy of combined androgen blockade with the GnRH analogues goserelin and buserelin with or without flutamide 750 mg/day have failed to demonstrate a significant response or survival advantage (see reviews by Brogden & Chrisp 1991; Chrisp & Goa 1991). The real survival benefit of combined GnRH analogue and antiandrogen therapy therefore remains unresolved. An ongoing randomised multicentre study involving 411 men with stage D_2 prostate cancer aims to evaluate the efficacy of combining leuprorelin with the newer nonsteroidal antiandrogen nilutamide (Crawford et al. 1990a,c). Preliminary results suggest a better objective response rate in the combined androgen blockade group (Crawford et al. 1990a).

The addition of flutamide to leuprorelin tended to produce a more rapid beneficial subjective response than the GnRH agonist alone. In the first

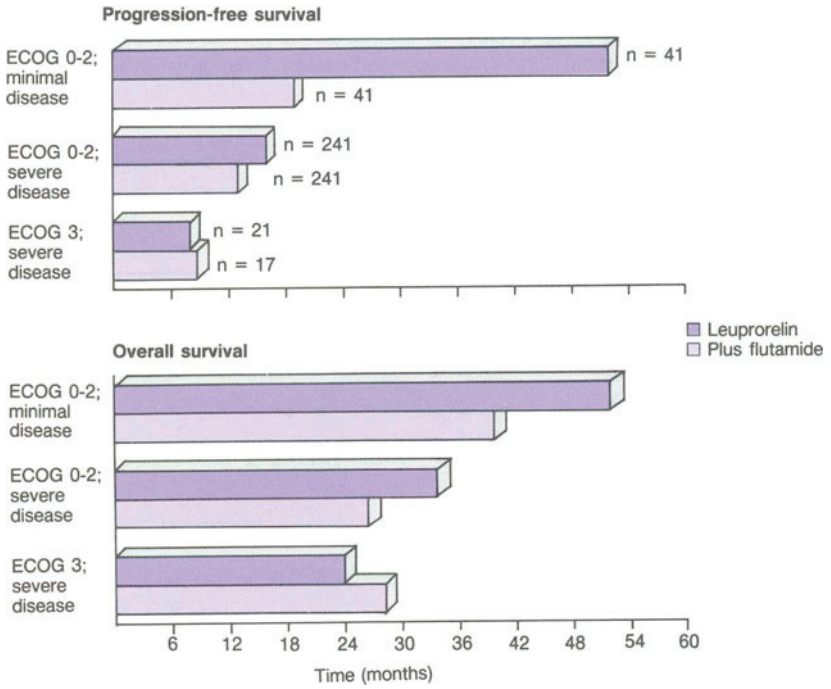

Fig. 5. Median progression-free and overall survival according to ECOG performance status and disease severity in patients with previously untreated stage D_2 prostatic cancer receiving subcutaneous leuprorelin 1 mg/day alone or plus flutamide 250mg 3 times daily (after Crawford et al. 1989, 1990b).

12 weeks of daily treatment, the odds for improvement in performance status and bone pain were greater with combination therapy (Crawford et al. 1989). Prolonged symptom-free survival also has been reported during treatment with other GnRH agonists plus flutamide (Brogden & Chrisp 1991; Chrisp & Goa 1991).

3.1.3 Leuprorelin Compared with Estrogens or Estramustine

Leuprorelin 1mg daily subcutaneously was equivalent to diethylstilbestrol 1mg 3 times daily orally in previously untreated men with stage D_2 prostate cancer, and monthly depot leuprorelin 3.75mg was equivalent to fosfestrol (diethylstilbestrol diphosphate) 100mg 3 times daily in patients with stage B, C or D disease (table III). Each agent delayed progression in 85 to 88% of patients, with a similar duration of response and overall survival; 87% of leuprorelin and 78% of diethylstilbestrol recipients were alive after 1 year of treatment (Leuprolide Study Group 1984). Disease progressed in 11% of evaluable leuprorelin-treated patients and in 2% of the diethylstilbestrol group remaining in the Leuprolide Study Group (1984) trial after 3 months' treatment, but this apparent difference in rate was attributed to more treatment withdrawals due to estrogenic toxicity than to leuprorelin adverse events (3 *vs* 12). A similar finding occurred in a subset of 23 patients participating in the Leuprolide Study Group trial (Winfield & Trachtenberg 1984). Indeed, although leuprorelin and estrogen treatment had comparable efficacy, the GnRH analogue was associated with a significantly enhanced tolerability profile (see section 4). This is also the case with other GnRH analogues, such as goserelin (Chrisp & Goa 1991).

De La Grange (1987) reported a slightly improved efficacy and similar tolerability for estramustine compared with leuprorelin in 2 groups of 30 patients after 1 year's treatment. Moreover, a combination of the 2 drugs produced significantly

Table III. Some randomised studies comparing subcutaneous leuprorelin (L) administration with oral diethylstilbestrol (DES) or fosfestrol (FOS) in patients with previously untreated prostatic cancer

Reference	No. of evaluable patients [mean age (years)]	Treatment [duration (months)]	Subjective response rate[a]	Objective response rate (%)[b]			Median duration of response (months)	Median survival (months)	Efficacy
				CR	PR	NC			
Leuprorelin 1 mg/day *vs* diethylstilbestrol 1mg tid									
Leuprolide Study Group (1984); Smith (1988)	92 (69)	L [1-26 (med 16.6)]	Bone pain, 32/44; PS, 41%	1	37	48	13.8	31.4	L = DES
	94 (71)	DES [0.5-26 (med 16.8)]	Bone pain, 33/48; PS, 36%	2	44	39	14.1	34.4	
Leuprorelin 3.75mg depot q4w *vs* fosfestrol 100mg tid									
Aso et al. (1991)	62 (75)	L (3)		0	19	68			L = FOS
	58 (72.5)	FOS (3)		0	24	64			

a In evaluable symptomatic patients.
b According to NPCP criteria.
Abbreviations and symbols: CR = complete response; PR = partial response; NC = no change, stable disease; PS = ECOG performance status; med = median; tid = 3 times daily; q4w = every 4 weeks; = indicates equivalent efficacy.

improved responses compared with each agent alone. Details of the response rates and regimens used were however lacking in this report, and these results await confirmation.

3.2 Treatment of Benign Prostatic Hypertrophy

Benign hyperplasia of the prostate is associated with obstructive voiding symptoms including reduced urinary flow rate, hesitancy and dribbling, and irritative symptoms such as nocturia, frequency and urge incontinence (Brendler 1990; Chodak 1990). The subjective importance placed on these troublesome symptoms is the primary indication for treatment, although chronic urinary tract infections, acute urinary retention and hydronephrosis also warrant intervention. The usual treatment of benign prostatic hypertrophy is surgery, either transurethral or, for tissue mass ≥ 70 to 80g, open prostatectomy. These procedures are invariably successful in relieving obstructive (but not irritative) symptoms and are rarely complicated. However, surgery may be contraindicated in some patients, for example those with bleeding disorders or susceptibility to anaesthetics (Brendler 1990). Leuprorelin and other GnRH agonists have a potential role, either in patients who are not candidates for surgery or perhaps as adjuvant therapy to shrink the hypertrophic prostate prior to surgery (Decensi et al. 1988). Interestingly, up to 57% of placebo-treated patients show clinical improvement (Matzkin & Braf 1991), emphasising the need for double-blind, placebo-controlled trials of leuprorelin in this indication.

Prostate size, determined by transrectal ultrasonography, declined by about 20% within the first 2 months of daily subcutaneous treatment with leuprorelin 1mg in groups of 3 to 15 men of mean age 73 to 83 years (Gabrilove et al. 1987, 1989; Levine et al. 1989; Schlegel & Brendler 1989). Shrinkage continued, with prostate size reaching a mean of 51g after 6 months, 55% of the pretreatment volume (Gabrilove et al. 1989; Schlegel & Brendler 1989). The decrease in prostate size was paralleled by a decline in serum testosterone to 0.5 nmol/L, dihydrotestosterone to 0.2 nmol/L and estradiol to 22 pmol/L after 4 months in 15 men (Gabrilove et al. 1989), and a reduction in mean serum prostate specific antigen level from 11.5 to 0.75 μg/L after 6 months in 12 others (Levine et al. 1989). Involution of prostatic epithelium appears to be the main cause of prostate shrinkage (Levine et al. 1989; Schlegel & Brendler 1989).

The mean score of obstructive symptom severity (0 = absent, 4 = severe) decreased from 1.7 to 0.1 within 4 months in 10 of 15 patients during daily subcutaneous treatment with leuprorelin 1mg; symptoms were absent in 9 patients (Gabrilove et al. 1989). Three of 5 men with indwelling catheters regained the ability to urinate normally within 3 to 5 months (Gabrilove et al. 1989). Six others with urinary retention were able to void spontaneously after 1 month's leuprorelin therapy, but with mean residual urine volumes of 187ml (Schlegel & Brendler 1989). Irritative symptoms were less well controlled, decreasing in mean severity from 2.6 to 2.1; there was no change in 7 of 10 patients (Gabrilove et al. 1989). Symptom control persisted during 1 to 3 years' daily leuprorelin treatment (Gabrilove et al. 1987, 1989). Within 4 months of stopping leuprorelin therapy, the prostate of 1 patient had regrown to its pretreatment size (Gabrilove et al. 1989). Concomitant use of the androgen fluoxymesterone, given in an attempt to minimise loss of libido and hot flushes (see section 4), apparently interfered with leuprorelin-induced prostate shrinkage in another patient (Gabrilove et al. 1989).

4. Tolerability

The sex hormone changes which occur during leuprorelin therapy are the cause of most of the unwanted symptomatic effects of the drug.

Impotence and decreased libido were almost universal in previously sexually active men within 3 months of starting daily or depot leuprorelin treatment (Gabrilove et al. 1989; Rizzo et al. 1990; Vance & Smith 1984; Winfield & Trachtenberg

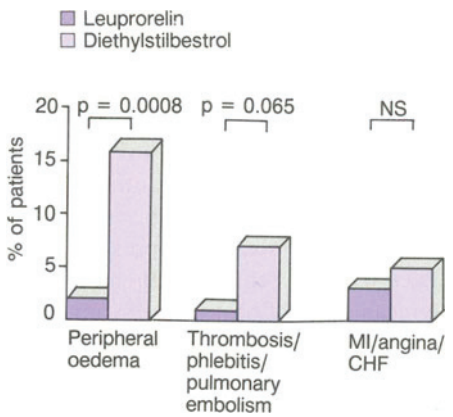

Fig. 6. Incidence of cardiovascular adverse effects in patients with prostatic cancer receiving leuprorelin 1 mg/day subcutaneously (n = 98) or diethylstilbestrol 1mg 3 times daily orally (n = 101) for up to 114 weeks; NS = not significant; MI = myocardial infarction; CHF = congestive heart failure (adapted from Leuprolide Study Group 1984).

1984), although Sharifi et al. (1990) reported an unusually low incidence of 5% with intramuscular leuprorelin 7.5mg. Hot flushes, often with sweating, were also very common, occurring in between 35 and 71% (mean 57%) of patients (Bischoff et al. 1990; Crawford et al. 1989; Leuprolide Study Group 1984; O'Brien & Hibberd 1990; Rizzo et al. 1990; Sharifi et al. 1990; Vance & Smith 1984). Flushing was usually mild and tolerable (Rizzo et al. 1990; Sharifi et al. 1990), and was significantly more frequent than with diethylstilbestrol 1mg 3 times daily (51% *vs* 11%; $p < 0.00001$) [Leuprolide Study Group 1984].

Importantly, however, leuprorelin has been associated with fewer adverse cardiovascular effects than diethylstilbestrol (fig. 6). Other investigators reported an absence of such events with leuprorelin (O'Brien & Hibberd 1990; Smith et al. 1985) or peripheral oedema in only 5 or 12.5% of patients (Crawford et al. 1989; Sharifi et al. 1990). Adverse effects occurred in 64% of leuprorelin and 95% of fosfestrol recipients in one study (Aso et al. 1991). Furthermore, fibrin generation was reduced by 15% and fibrinolytic activity increased by 30% in 23 women with endometriosis receiving leuprorelin or buserelin (Winkler et al. 1990). Thus, despite similar efficacy (see section 3.1.3), leuprorelin is associated with fewer potentially serious cardiovascular reactions than estrogens. Moreover, gynaecomastia which is troublesome rather than dangerous, occurred in 3% of patients receiving leuprorelin 1 mg/day compared with 49% of diethylstilbestrol recipients (Leuprolide Study Group 1984). Rizzo et al. (1990) reported a 16% incidence of gynaecomastia in 43 patients receiving depot leuprorelin treatment, and Bischoff et al. (1990) noted occasional nipple hypersensitivity.

Leuprorelin has also been associated with mild nausea and vomiting in 5 to 14% of patients, and mild diarrhoea in 5% (Crawford et al. 1989; Leuprolide Study Group 1984; Rizzo et al. 1990). Minor irritation at the injection site during daily subcutaneous administration has occurred (Smith et al. 1985) and local reactions, including pain, nodule formation (probably fibrosis), pruritus and necrosis, were reported in 2 to 3% of patients receiving monthly subcutaneous depot injections (Bischoff et al. 1990; O'Brien & Hibberd 1990).

Leuprorelin administration is associated with an initial transient elevation in serum testosterone levels at the beginning of treatment (section 1.2), which caused an exacerbation or 'flare' of symptoms in between 4 and 29% (usually approximately 10%) of patients during the first 2 weeks of treatment (Niijima et al. 1990; O'Brien & Hibberd 1990; Smith et al. 1985; Trachtenberg 1983). Flare was most often manifested as localised bone pain or back pain, but weakness and/or paraesthesia, spinal cord compression, and dysuria and flank pain resulting from ureteric occlusion may occur in patients with prostate cancer (O'Brien & Hibberd 1990; Wojciechowski et al. 1986), and obstructive symptoms may worsen in those with benign hyperplasia (Schlegel & Brendler 1989). Symptoms usually began within 1 to 4 days after initiation of leuprorelin treatment and had subsided spontaneously within 2 weeks. However, Johns et al. (1990) demonstrated scintigraphic evidence of flare on bone scan in 5 of 26 patients after 3 to 6 months of daily subcutaneous leuprorelin administration. Thompson et al. (1990) reported 2 sudden deaths

during disease flare associated with starting GnRH therapy, and retrospectively identified 15 similar cases among 765 patients participating in clinical trials of a variety of these agents. Spinal cord compression did not appear to be the cause of death.

Adding an antiandrogen appears to alleviate symptom flare to some extent. The severity of pain exacerbation was reduced in 303 men given concomitant flutamide 250mg 3 times daily compared with 300 others receiving leuprorelin alone (Crawford et al. 1989), and flare was not apparent in 18 patients receiving nilutamide 100mg 3 times daily for the first 2 weeks of leuprorelin treatment (Navratil 1990). Similarly, diethylstilbestrol 1mg 3 times daily for 1 week before and 1 week after beginning daily leuprorelin therapy in 9 men blunted the surge of testosterone synthesis; testosterone levels increased to a maximum of 14.5 nmol/L (*vs* 14 to 23 nmol/L without diethylstilbestrol coadministration) after 3 days' GnRH agonist administration, and declined to 5 nmol/L within a week (Stein & Smith 1985) [section 1.2].

5. Dosage and Administration

In patients with prostate cancer or benign prostatic hypertrophy, leuprorelin used to be self-administered as a daily subcutaneous 1mg injection. This route is, however, now eclipsed by a sustained release biodegradable 3.75 or 7.5mg depot formulation, injected once every 4 weeks subcutaneously or intramuscularly without a local anaesthetic using a 22 or 23 gauge needle. To minimise local reactions, the injection site should be varied periodically.

Caution is recommended in administering leuprorelin to prostate cancer patients at risk from spinal cord compression or ureteric obstruction during the first 2 weeks of therapy. Alternatively, another method of androgen ablation should be considered in such patients. Coadministration of an antiandrogen or diethylstilbestrol 1mg 3 times daily for 1 week before and 1 week after the initial leuprorelin dose may diminish symptom flare.

6. Place of Leuprorelin in Therapy

When used as palliative treatment in men with previously untreated androgen-sensitive prostatic cancer, leuprorelin is as effective as diethylstilbestrol in preventing disease progression and prolonging survival, but has a significantly improved tolerability profile (see also review by Henriksson 1991). Nevertheless, more studies are needed to fully assess how leuprorelin compares with estrogen therapy, since the only comparison with diethylstilbestrol (Leuprolide Study Group 1984) excluded early death and early progression (i.e. within 3 months) from the estimation of time to objective relapse, and follow-up could have been longer. Comparisons between leuprorelin and orchidectomy are unfortunately lacking; however, results obtained with other GnRH agonists, notably goserelin and buserelin, reveal equivalent efficacy with the advantage of avoiding the morbidity and psychological stress often associated with surgical castration (Soloway et al. 1991; see reviews by Brogden et al. 1990; Chrisp & Goa 1991). There is some evidence that complete androgen blockade achieved with coadministration of an antiandrogen such as flutamide may improve survival, particularly in patients with good performance status and few metastases, compared with leuprorelin alone. This area does require additional clarification however, since several other well-controlled long term studies indicate no survival benefit in adding flutamide to a GnRH agonist regimen (Brogden & Chrisp 1991; Iversen et al. 1990; Keuppens et al. 1990). Concurrent flutamide, or perhaps diethylstilbestrol, nevertheless appears to minimise the risk of symptom flare during the first few weeks of leuprorelin treatment.

Leuprorelin has limited clinical benefit in castrated patients where the major site of action of the drug, the testes, has been removed. Patients refractory to pharmacological hormone therapy such as diethylstilbestrol also usually do not respond to subsequent leuprorelin treatment, despite suppression of testicular testosterone synthesis to castrate levels.

Leuprorelin shrinks hyperplastic tissue in men

with benign prostatic hypertrophy and may thus alleviate obstructive symptoms, although a considerable placebo response has been noted (Matzkin & Braf 1991). Furthermore, continuous leuprorelin therapy is necessary to maintain remission; in contrast, the usual treatment for benign hypertrophy, transurethral prostatectomy, is a once-only procedure with a high success rate. Reserving leuprorelin (and other GnRH agonists) therapy for those men who are not surgical candidates, or as an adjuvant for preoperative tissue shrinkage, has therefore been suggested. Long term use of GnRH agonists may become more widespread to avoid postoperative morbidity: 24% of 263 men undergoing prostatectomy (usually considered a low risk operation) experienced complications within 3 months of surgery; 20% had an infection (Fowler et al. 1988). The high cost of performing so many operations should also be considered (Matzkin & Braf 1991).

Leuprorelin is thus a safer alternative to estrogens, and may be preferred by some to orchidectomy, in the management of men with advanced prostate cancer. Adding an antiandrogen may further prolong survival, but this aspect remains unresolved. In men with benign prostatic hypertrophy, leuprorelin induces symptom remission and may be used to avoid surgical complications. This GnRH agonist, in common with other members of this class, is therefore a reasonable nonsurgical alternative in patients with prostatic disorders associated with aging.

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