Leuprorelin: a leading role in advanced prostate cancer therapy

Raj Persad

Leuprorelin is a luteinizing hormone-releasing hormone analogue, licensed in the UK for the treatment of advanced prostate cancer. This review highlights the efficacy and tolerance of this agent and the benefits provided for developing patient-centred therapy and optimizing patient quality of life.

Prostate cancer is one of the most common types of cancer in men aged 65 years and over and a common cause of death in this age group (Persad, 2002). Over the past few years, screening programmes using prostate-specific antigen (PSA) levels have increased the detection of early stage disease, which is often treatable using radical prostatectomy or radiotherapy. However, many cases are undiagnosed until symptoms appear, at which point the disease is often locally advanced or metastatic. For these patients, and those with recurrent cancer, androgen suppression is standard care (Hamm et al, 2000).

MANAGEMENT OF ADVANCED DISEASE

The growth of prostate cancer cells is stimulated by androgens. Androgen suppression is one approach used in prostate cancer management (antiandrogens are also used which rely on blockade of the receptor) (Debruyne and Dijkman, 1995). Orchiectomy, while an effective means of androgen suppression, is often problematic for patients from a psychological perspective. An important current therapy for locally advanced or metastatic prostate cancer is medical castration by regular injections of luteinizing hormone-releasing hormone (LHRH) analogues such as leuprorelin, buserelin and goserelin (Fornara and Jocham, 1996). These agents have to be injected as poor absorption from the gastrointestinal tract renders them inactive when administered orally.

LHRH analogues inhibit luteinizing hormone production, which in turn suppresses testosterone production. Survival following LHRH analogue therapy is equivalent to that following orchiectomy, and better than monotherapy with non-steroidal antiandrogens (Seidenfeld et al, 2000). The current management of advanced prostate cancer involves early initiation of LHRH analogue therapy (as soon as metastatic or locally advanced prostate cancer is diagnosed) rather than waiting for the onset of symptoms (Newling, 2001).

Androgen suppression does not cure prostate cancer, but it does delay clinical progression and improve symptoms (e.g. bladder outflow obstruction, pathological fractures, metastatic bone pain) in most patients. Even with continued suppression of testosterone, relapse eventually occurs as a result of the growth of androgen-independent tumour cells (Persad, 2002).

Quality of life is an important issue in the management of advanced prostate cancer (Fossa, 1996), and the need for individualized, patient-orientated treatment has been noted (Wechsel et al, 1996). In the case of injected therapy for advanced prostate cancer, minimizing patient distress, discomfort and injection site trauma while maximizing patient choice and convenience are important aims if quality of life is to be optimized.

Leuprorelin acetate (Prostap, Wyeth Pharmaceuticals, Taplow) is a leading depot LHRH analogue (Persad, 2002). It has been in clinical use in the management of prostate cancer in Europe since 1989; during this time it has been extensively studied and undergone continued development to maximize convenience of administration for patients and health-care professionals.

CHEMISTRY AND PHARMACY

Natural LHRH was isolated in 1971, followed by the synthesis of leuprorelin (a synthetic nonapeptide analogue of porcine LHRH) in 1974. Leuprorelin has a longer half-life than natural LHRH owing to its enhanced binding affinity and resistance to enzymic degradation, and is 80 times more potent than natural LHRH (Wojciechowski et al, 1986; Persad, 2002). Leuprorelin suppresses androgens by sustained occupation of pituitary gonadotrophin-releasing hormone (GnRH) receptors, which causes down-regulation of receptors in

Mr Raj Persad is Consultant Urologist at Bristol Royal Infirmary, Bristol BS2 8HW and an Honorary Senior Clinical Lecturer at University of Bristol

the anterior pituitary. This suppresses gonadotrophin release and reduces testosterone release by the testes to castrate levels (Wojciechowski et al, 1986; Chrisp and Sorkin, 1991). Leuprorelin may also act directly as a negative growth factor on prostate cancer cells, regulating cell growth and PSA gene expression (Sica et al, 1999).

Microsphere technology

Advances in biodegradable polymers and microsphere technology have enabled the development of leuprorelin as monthly intramuscular or subcutaneous depot injections, and a 3-monthly subcutaneous injection. This means that leuprorelin can be given less often, with potential advantages in patient compliance and greater convenience for both patients and health-care professionals. The 3-month depot formulation, for example, reduces the total number of injections to four per year, which can be timed to coincide with other check-ups (Persad, 2002). This reduction in the number of injections and consultations may reduce distress in patients who are often elderly and have co-morbid conditions (Wechsel et al, 1996).

The 1-month depot formulation consists of leuprorelin incorporated into a controlled-release biodegradable lactic and glycolic acid copolymer formed into microspheres (mean size 20 μm). The 3-month depot formulation consists of leuprorelin incorporated into a polylactic acid copolymer formed into microspheres (mean size 10–30 μm) (Persad, 2002). The microspheres can be administered as a liquid injection through a fine-gauge needle without needing local anaesthetic or special injection techniques (Persad, 2002).

PHARMACOKINETICS

1-month depot

After injection of the 1-month depot formulation of leuprorelin, peak serum levels are achieved within 1 hour, followed by a rapid fall over the next 24 hours (Persad, 2002). Leuprorelin levels of 200–287 pg/ml are then maintained for at least 5 weeks (Wechsel et al, 1996). Over a 45-month treatment period, repeated monthly injections result in constant therapeutic levels with no evidence of leuprorelin accumulation.

3-month depot

After injection of the 3-month depot formulation of leuprorelin, a similar initial rise in serum leuprorelin levels occurs (Persad, 2002). The plateau phase is reached at about 7 days, and constant serum concentrations are maintained for at least 3 months (Wechsel et al, 1996). As with the monthly depot injections, there is no evidence of drug accumulation with long-term therapy.

Effect on testosterone levels

An optimum therapeutic effect on androgen-dependent prostate cancer cells is achieved by reducing serum testosterone levels to castrate levels (≤50 mg/dl). ('Chemical castration' is achieved in which testosterone secretion by the testes is suppressed by the LHRH analogue. This means that the hormonal stimulation of prostate cancer cells is 'switched off'. The effect is achieved in hormone-sensitive cells, which account for the majority, but there are always some insensitive cells which means that in time hormone resistance can occur.) This can be achieved by 1-month depot injections of leuprorelin 3.75 mg, or by 3-month depot injections of leuprorelin 11.25 mg (*Figure 1*) (Wechsel et al, 1996; Persad, 2002). All LHRH analogues cause an initial rise in testosterone levels after the first injection, but castrate levels are achieved in 3–4 weeks and are maintained throughout treatment (Chrisp and Sorkin, 1991).

CLINICAL EFFICACY

Early studies in patients with metastatic or advanced prostate cancer established the efficacy of daily subcutaneous injections of leuprorelin in suppressing testosterone levels, delaying tumour progression and alleviating symptoms (Glode, 1982; Trachtenberg, 1983; Smith, 1984; Yamanaka et al, 1984; Imai et al, 1985; Periti et al, 1987). Further data are available from studies using the 1-month and 3-month depot formulations.

A review by Persad (2002) of studies of the 1-month leuprorelin depot injection in patients with metastatic or locally advanced prostate cancer revealed that serum testosterone fell to castrate levels within the first month and remained at this level throughout therapy (up to about 5 years). Symptoms (bone pain and urinary symptoms) were reduced, performance status improved or stabilized and PSA levels fell. During follow up of up to 2 years, disease progression was prevented in up to 95% of patients. No differences were reported between subcutaneous and intramuscular administration (Bischoff, 1990).

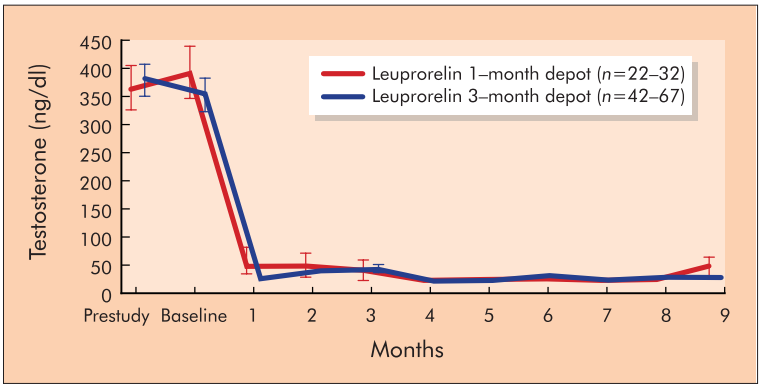

Figure 1. Suppression of plasma testosterone by leuprorelin depot injection, 3.75 mg 1-month or 11.25 mg 3-month injection, over 9 months. From Persad (2002).

A randomized, open-label comparative study of the efficacy, safety and tolerability of leuprorelin 1- and 3-month depot found similar results with the two formulations (Wechsel et al, 1996). Treatment in 237 patients with locally advanced or metastatic prostate cancer for 9 months with either the 1-month 3.75 mg formulation or the 3-month 11.25 mg formulation produced similar clinical response and tolerability (*Figure 2*).

The long-term efficacy and safety of 3-month leuprorelin injections in treating advanced prostate cancer was confirmed in a study in which 37 patients received the 3-month formulation for up to 43 months (Jocham, 1998). Serum testosterone was suppressed to castrate levels throughout, with adverse events similar to those reported previously. Prospective data obtained during this study indicated that the median survival time from the beginning of therapy was 3.1 years, with a median time to tumour progression of 2.8 years.

COMPARISON WITH OTHER LHRH ANALOGUES

Meta-analysis of data from ten studies involving 1908 patients treated with LHRH analogues revealed no difference in overall survival between patients treated with the LHRH analogues leuprorelin, goserelin and buserelin (Seidenfeld et al, 2000). Another study, however, indicated that while the three analogues had similar clinical effects, leuprorelin produced a greater reduction in PSA levels than the other two (Bono et al, 1996).

Patient acceptability may vary between different analogues because of different administration methods. Leuprorelin and triptorelin microspheres are injected using a fine-gauge needle, while goserelin is implanted as a depot pellet via a larger gauge needle (Beese, 2000). Anecdotal evidence suggests that patients prefer leuprorelin injections to goserelin implants because the finer needle minimizes discomfort and injection site trauma.

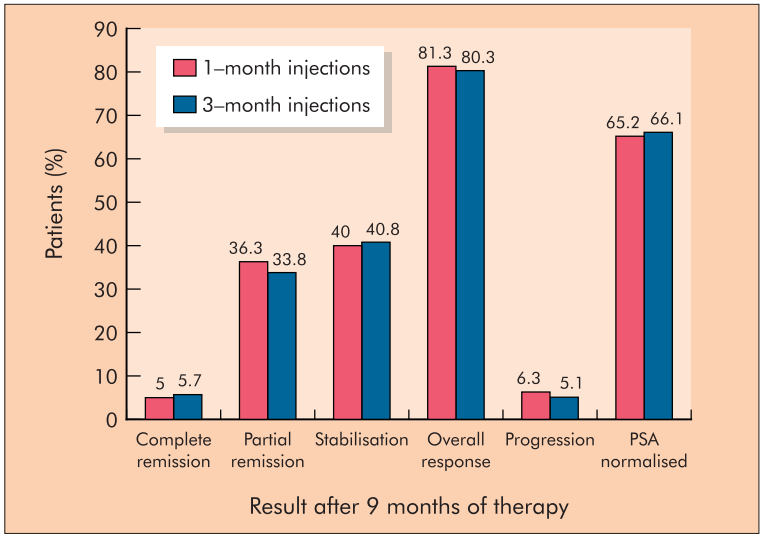

Figure 2. Comparative efficacy of 9 months of treatment with 1- and 3-month leuprorelin depot formulations (Wechsel et al, 1996). PSA = prostate-specific antigen.

SAFETY AND TOLERABILITY

LHRH analogues are generally well tolerated; during clinical studies, withdrawal rates of 0–4% were reported compared with 4–10% for non-steroidal antiandrogen therapies (Seidenfeld et al, 2000). While a progressive reduction in bone density occurs over time with continuous androgen deprivation, this is less than that observed with orchiectomy (Kiratli et al, 2001). Pamidronate can be used to prevent this bone loss in men receiving leuprorelin for prostate cancer (Smith et al, 2001).

Both 1- and 3-month leuprorelin formulations have good tolerability profiles. The side effects experienced by patients are similar and as expected with androgen suppression, with hot flushes, increased sweating and reduced libido most commonly reported (*Table 1*) (Wechsel et al, 1996). When assessed, 87.5% of patients receiving 1-month and 83.4% of patients receiving 3-month leuprorelin injections rated their medication as 'well tolerated' or 'very well tolerated' (Wechsel et al, 1996). Less common side effects include gynaecomastia, peripheral oedema, fatigue, nausea, headache, arthralgia, dizziness, insomnia, paraesthesia, visual disturbances and weight change. In clinical trials most side effects have been mild to moderate and withdrawal rates have been low. Irritation at the injection site occurs in about 3% of patients (O'Brien and Hibberd, 1990).

As with other LHRH analogues, initial administration of leuprorelin is associated with a transient increase in testosterone levels, which can exacerbate symptoms in up to 30% of patients (O'Brien and Hibberd, 1990; Chrisp and Sorkin, 1991). This 'flare' subsides with continued therapy.

FUTURE DIRECTIONS

The place of LHRH analogues in prostate cancer therapy continues to develop alongside other agents in continuous and intermittent therapy regimens as well as a neoadjuvant or adjuvant to radiotherapy for early or locally advanced prostate cancer. They have been used in maximal androgen blockade to reduce residual testosterone production by the adrenal glands, and as neoadjuvant and adjuvant therapy in patients undergoing radical treatment for localized and locally advanced prostate cancer (Crawford et al, 1989; Debruyne and Dijkman, 1995; Tyrell, 1999). New formulations are under development, including 6- and 12-month formulations. These advances, plus the potential for patient self-injection (Hamm et al, 2000), would add further flexibility to an already convenient and adaptable administration system.

CONCLUSIONS

Medical castration using injected LHRH analogues is one of the mainstays of therapy for locally advanced and metastatic prostate cancer. The efficacy of the available LHRH analogues in suppressing testosterone to castrate levels is similar, and tolerability of these agents is generally good. Leuprorelin offers the advantage of administration by liquid injection (using a fine-gauge needle that minimizes patient discomfort and injection site trauma) by any member of the health-care team without specialized training, and has potential for patient self-administration. Leuprorelin also offers a choice of injection frequencies (1-month and 3-month), which can be timed to coincide with regular check-ups. **HM**

Conflict of interest: Mr Persad wrote this article at the invitation of Wyeth Pharmaceuticals. The views expressed in this article are based on the clinical experience of Mr Persad and are not necessarily those of Wyeth Pharmaceuticals.

Beese G (2000) Randomised cross over trial to assess the tolerability of LHRH analogue administration. Abstract. British Association of Urological Nurses Summer Conference and Annual General Meeting, Birmingham, 19 June: 8–10

Bischoff W (1990) 3.75 and 7.5 mg leuprorelin acetate depot in the treatment of advanced prostatic cancer: preliminary report. German Leuprorelin Study Group. *J Int Med Res* **18** (suppl 1): 103–13

Bono AV, Brausi M, Bartolotta G, Catanzaro F, Civino G (1996) Chemical castration with different LH-RH analogues. *Eur Urol* **30** (suppl 2): 525

Chrisp P, Sorkin EM (1991) Leuprorelin. A review of its pharmacology and therapeutic use in prostatic disorders. *Drugs Aging* **1:** 487–509

Crawford ED, Eisenberger MA, McLeod DG et al (1989) A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* **321:** 419–24

Debruyne FMJ, Dijkman GA (1995) Advances and trends in hormonal therapy for advanced prostate cancer. *Eur Urol* **28:** 177–88

Fornara P, Jocham D (1996) Clinical study results of the new formulation leuprorelin acetate three-month depot for the treatment of advanced prostate carcinoma. *Urol Int* **56** (suppl 1): 18–22

Fossa SD (1996) Quality of life in prostate cancer: what are the issues and how are they measured? *Eur Urol* **29** (suppl 2): 121–3

Glode LM (1982) Leuprolide therapy of advanced prostatic cancer. *Proc ASCO* **1:** C-426

Hamm R, Patel B, Whittlestone R, Persad R (2000) Patient self-injection: a new approach to administering luteinizing hormone-releasing hormone analogues. *Br J Urol Int* **86:** 840–2

Imai K, Kumasaka F, Kobayashi M et al (1985) [Hormonal and clinical efficacy of (D-Leu6)-des Gly-NH2(10)-LHRH ethylamide against prostatic cancer]. *Hinyyokika Kiyo* **31**(12): 2302–6

Jocham D (1998) Leuprorelin three-month depot in the treatment of advanced and metastatic prostate cancer: long-term follow-up results. *Urol Int* **60** (suppl 2): 18–24

Kiratli BJ, Srinivas S, Perkash I, Terris MK (2001) Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. *Urology* **57:** 127–32

Newling D (2001) Advanced prostate cancer: immediate or deferred hormone therapy? *Eur Urol* **39** (suppl 1): 15–21

O'Brien A, Hibberd M (1990) Clinical efficacy and safety of a new leuprorelin acetate depot formulation in patients with advanced prostatic cancer. *J Int Med Res* **18** (suppl 1): 57–68

Periti P, Rizzo M, Mini E et al (1987) Preliminary results of a Phase II multicentre study on the clinical efficacy and safety of the LHRH analog leuprolide in the treatment of prostatic carcinoma. *J Endocrinol Invest* **129:** 1149–52

Persad R (2002) Leuprorelin acetate in prostate cancer: a European update. *Int J Clin Pract* **56:** 389–96

Seidenfeld J, Samson DJ, Hasselblad V et al (2000) Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* **132:** 566–77

Sica G, Iacopino F, Settesoldi D, Zelano G (1999) Effect of leuprorelin acetate on cell growth and prostate-specific antigen gene expression in human prostate cancer cells. *Eur Urol* **35** (suppl 1): 2–8

Smith JA Jr (1984) Androgen suppression by a gonadotropin releasing hormone analogue in patients with metastatic carcinoma of the prostate. *J Urol* **131**(6): 1110–12

Smith MR, McGovern FJ, Zietman AL et al (2001) Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* **345**: 948–55

Trachtenberg J (1983) The treatment of metastatic prostatic cancer with a potent luteinizing hormone releasing hormone analogue. *J Urol* **129**(6): 1149–52

Tyrell CJ (1999) Adjuvant and neoadjuvant hormonal therapy for prostate cancer. *Eur Urol* **36:** 549–58

Wechsel HW, Zerbib M, Pagano F, Coptcoat MJ (1996) Randomized open labelled comparative study of the efficacy, safety and tolerability of leuprorelin acetate 1M and 3M in patients with advanced prostatic cancer. *Eur Urol* **30** (suppl 1): 7–14

Wojciechowski NJ, Carter CA, Skoutakis VA, Bess DT, Falbe WJ, Mickle TR (1986) Leuprolide: a gonadotropin-releasing hormone analog for the palliative treatment of prostate cancer. *Drug Intell Clin Pharm* **20:** 746–51

Yamanaka H, Makino T, Kumasaka F, Shida K (1984) [Clinical efficacy of (D-Leu6)-des Gly-NH2(10)-LHRH ethylamide against prostatic cancer]. *Hinyokika Kiyo* **30**(4): 545–60

TABLE 1.
Side effects experienced by patients receiving leuprorelin depot injections over 9 months

	Patients experiencing side effect (%)	
Side effect	1-month leuprorelin 3.75 mg (*n*=80)	3-month leuprorelin 11.25 mg (*n*=157)
Hot flushes	60.0	47.8
Increased sweating	42.5	36.3
Decreased libido	28.8	23.6
Atrophy of testicles	30.0	21.0
Impotence	23.8	22.3
Skeletal pain	12.5	14.0
Muscle weakness	15.0	10.8
Urinary tract infection	16.3	8.9
Fatigue	10.0	12.1
Nocturia	10.0	11.5
Anorexia	7.5	11.5
Dysuria	10.0	8.3

From Wechsel et al (1996)

KEY POINTS

- Leuprorelin is an effective and well-tolerated luteinizing hormone releasing hormone (LHRH) analogue used for androgen suppression.
- Clinical trials have demonstrated that all LHRH analogues have similar efficacy and tolerability.
- Leuprorelin provides a number of benefits for developing patient-centred therapy and optimizing patient quality of life.
- Leuprorelin can be administered by liquid injection (minimizing patient discomfort and injection site trauma) by any member of the health-care team without specialized training.
- Leuprorelin offers a choice of injection frequencies (1-month and 3-month), which can be timed to coincide with regular check-ups.