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BRIEF REVIEW

Effect of a new leuprorelin formulation on testosterone levels in patients with advanced prostate cancer

R. Berges [a] and U. Bello [b]

[a] *PAN-Klinik am Neumarkt, Cologne, Germany*

[b] *Astellas Pharma Europe Ltd, Staines, UK*

Address for correspondence: **Richard Berges, Zeppelin Straße 1, 50667 Cologne, Germany. Tel: +49 221 277 6280; Fax: +49 221 277 6289; email: R.Berges@PAN-Klinik.org**

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ABSTRACT

Background and scope: Leuprorelin is a well known luteinising hormone releasing hormone (LHRH) agonist. The drug is effective in the treatment of advanced prostate cancer and is well tolerated. This article reviews published literature (based on a search of PubMed, EMBASE and Biosis databases to the end of 2005) and other sources of data on a new formulation of leuprorelin acetate (Eligard*) for use in the treatment of hormone-dependent advanced prostate cancer. This product takes advantage of a novel delivery system (Atrigel†) which forms an implant *in situ* that is capable of delivering double doses of leuprorelin consistently to provide better, more sustained testosterone suppression compared with a microsphere leuprolide acetate formulation. Two formulations, 7.5 mg and 22.5 mg, are currently available with duration of action of 1 and 3 months, respectively. The 2-week stability at room temperature prior to mixing facilitates its use and reduces the potential for waste.

Findings: In clinical studies of the new leuprorelin acetate formulation reviewed here, all patients achieved testosterone levels ≤ 50 ng/dL and up to 98% of patients showed levels comparable to those resulting from surgical bilateral orchidectomy (≤ 20 ng/dL). Both formulations showed minimal breakthroughs, defined as a rise in testosterone levels after reaching levels of 50 ng/dL. The safety profile is typical of LHRH agonists, with mild to moderately severe 'hot flushes' being the most common adverse event. The higher dose of 22.5 mg, with a volume of 0.375 mL is administered subcutaneously via a small 20G needle, causing little local discomfort.

Conclusion: Prostate cancer remains a major cause of morbidity and mortality in older men. In the majority of cases, suppression of serum testosterone levels is very effective. The level of testosterone suppression is currently under debate, with ideal suppression levels ranging from 20 to 50 ng/dL. Not all LHRH agonist therapy achieves the same degree of testosterone suppression as bilateral orchidectomy. The new leuprorelin acetate (Eligard) appears to achieve a testosterone suppression of 20 ng/dL in 98% of patients, while maintaining a side effect profile comparable to other products in its class.

Introduction

The 5-year survival rate for metastatic prostate cancer continues to be as low as 31%[1], despite the availability of a choice of treatment modalities, including bilateral orchidectomy, or the use of luteinising hormone releasing hormone (LHRH) agonists. These have the net effect of reducing circulating testosterone

* Eligard is a registered trade name of Astellas pharma in Europe and the sanofi-aventis group of companies in the USA
† Atrigel is a registered trade mark of QLT USA, Inc., Fort Collins, CO, USA

concentration. Although the optimal concentration is still uncertain, serum testosterone levels are used as a surrogate marker for therapeutic success. LHRH agonists are effective but a minority of patients experience breakthroughs and/or acute-on-chronic responses. The clinical significance of these is still unclear.

This article reviews the effect of Eligard‡, a new formulation of leuprorelin, on serum testosterone levels. The review of the published literature is based on a search of PubMed, EMBASE and Biosis databases using search terms GnRH agonist, LHRH agonist, prostate cancer and testosterone for the period January 1980–August 2005, augmented by other sources of data including a Discussion Forum (25 June 2005, Paris, France) held during the 6th International Consultation on New Developments in Prostate Cancer and Prostate Diseases (ICNDPCPD).

Androgens and the prostate

The dependency of the prostate on androgens for its normal function has long been recognized. Testosterone is essential to the perpetuation of prostate cancer. Reducing the level of testosterone will diminish the size of the tumour and slow down its growth[2]. In an excellent review of the literature and work from his own laboratory, Schalken explores this relationship between prostate cancer and androgens[3]. Briefly, not all prostate cells are susceptible to androgen control. The secretory glandular cells secrete prostate fluid containing prostate specific antigen (PSA), prostate specific acid phosphate (PAP) and prostaglandins. They are androgen dependent for their secretory ability and viability. The stem cells are not androgen dependent for their survival but are androgen sensitive for cell proliferation. If androgen levels are restored, their proliferation is induced[4].

Ninety-five per cent of circulating testosterone is produced by the testes and testerone is the major circulating androgen in blood. In the prostate it is converted to 5α-dihydrotestosterone (DHT), which has a higher affinity for androgen receptors than testosterone. Both these androgens directly induce differentiation of prostate epithelial cells and, through growth factor production by the prostate stroma, indirectly effect transient proliferation. Androgens also directly stimulate angiogenesis through the production of vascular endothelial growth factor[3]. Androgen deprivation leads to apoptosis of all androgen dependent cells, including the secretory glandular cells[5]. Unfortunately, not all prostate cancer patients respond to long-term hormone therapy. The role of androgen receptors in prostate cancer needs to be further researched.

Optimizing testosterone levels

In the majority of cases, prostate cancer cells are dependent on testosterone and DHT for their growth and development. Indeed, in the absence of these hormones, androgen-dependent tumours may shrink or even disappear. For this reason, androgen withdrawal has been the main approach to managing prostate cancer for over 40 years. Ineffective androgen suppression therapy has been shown to result in higher prostate cancer mortality[6]. Bilateral orchidectomy has been considered as the gold standard of testosterone suppression[2]. Since the 1980s, chemical castration with LHRH agonists is an option which is often preferred by patients and physicians.

The goal of hormonal treatment in advanced or metastatic prostate cancer is to reduce serum testosterone levels. The definition of the optimal testosterone control is the subject of intensive debate. Many physicians continue to consider testosterone levels below 50 ng/dL as satisfactory. It is worth noting that 50 ng/dL was based on assay methods developed in the 1960s. Since then, modern techniques have been developed with a sensitivity permitting testosterone measurements as low as 10 ng/mL[2]. So what is the optimal testosterone level?

Increasingly, it is being argued that 'medical castration' should reduce testosterone to bilateral surgical orchidectomy levels[7] or even 'the lower the better'[8]. By using a chemiluminescent immunoassay method, Oefelein *et al.*[8] showed that after bilateral orchidectomy, median total testosterone was decreased to 15 ng/dL with a range from a minimum of < 10 to a maximum of 30 ng/dL. In these patients the levels rarely exceeded 20 ng/dL[9]. Other studies confirm that these levels are reached within 4 weeks of orchidectomy[10,11] and, in another study, within less than 12 h[12].

Zlotta and Debruyne report on the conclusions reached at an Expert Consensus Meeting (22 May 2005, San Antonio, USA) and a Discussion Forum (25 June 2005, Paris, France) during the 6th ICNDPCPD[13]. The experts agreed that, using orchidectomy as the benchmark, achieving a testosterone level below/equal to 20 ng/dL after LHRH agonist therapy would be desirable.

The experts did recognize that the relationship between testosterone levels and clinical outcome needs further clinical investigation. The interpretation

‡ Eligard is a registered trade name of astellas pharma in Europe and the sanofi-aventis group of companies in the USA

of currently available data is further complicated by an important inter- and intra-assay variability. The discussion was concluded that, given all circumstances being the same, achieving lower testosterone values is the optimal strategy.

At the Discussion Forum at the 6th ICNDPCPD, 80% of delegates agreed that the main goal of therapy is to achieve, 'the lowest possible level of testosterone', while 64% indicated that they would target levels ≤ 20 ng/dL[14].

LHRH agonist performance also needs to be judged by the ability to avoid any rises in testosterone levels after initial suppression. These breakthroughs could indicate therapy failure and, although data on the subject are not available, may have clinical consequences. The experts agreed that a rise in testosterone from a nadir to above 50 ng/dL, is considered to be clinically significant and should have implications for treatment[14].

While the absence of conclusive data leaves some important questions unanswered, the authors agree with the conclusions reached by the experts at the Experts Consensus Meeting in San Antonio.

It has been stated above that the goal of therapy is to reduce circulating testosterone levels. However, adrenal androgens can be converted to dihydrotestosterone (DHT) in the prostate. Formation of DHT is likely to be important in the induction and/or maintenance of prostate cancer[15]. Significant amounts of DHT are still present in prostatic tissue after castration[16]. For this reason, complete androgen blockade (CAB) using a combination of chemical or surgical castration with anti-androgens is an alternative approach to treating advanced prostate cancer[17]. Laufer *et al.* reviewed the literature comparing CAB to chemical or surgical castration alone. Twenty-seven prospective, randomized clinical studies with a total of 7987 patients were identified: only three supported CAB. The authors conclude that there is no support for the routine use of CAB as first line therapy in patients with metastatic prostate cancer[18].

LHRH agonist performance

The LHRH agonists currently on sale in Europe include leuprolide, buserelin, goserelin and triptorelin, each available in depot formulation requiring monthly or three-monthly injections. It is important to understand how these LHRH agonist preparations perform using this more up-to-date definition of testosterone control. This subject is reviewed in a recent publication by Tombal[14]. After reviewing a number of publications, Tombal concludes that between 5% and 17% of patients fail to achieve 50 mg/dL, while in 13–34% of patients the testosterone remains above 20 ng/dL. The publications reviewed included patients treated with a variety of LHRH agonists including leuprolide, goserelin and buserelin.

Tombal and Berges[19] also make a distinction between breakthrough responses and acute-on-chronic responses. Breakthrough responses are surges in testosterone to ≥ 50 ng/dL at any time during treatment and were reported with an incidence varying from 2 to 13% of patients on conventional LHRH agonists. Acute-on-chronic responses are increases in testosterone levels to ≥ 50 ng/dL, during long-term treatment, upon re-administration of the drug. In this literature review, acute-on-chronic responses occurred in 4–10% of the patients using conventional LHRH agonists. Zinner *et al.*[20] reported up to 23% of goserelin treated patients show acute-on-chronic responses (≥ 18.5 ng/dL). In this open label study, patients were treated with 3.6 mg (n = 129) or 10.8 mg (n = 118) of goserelin. Two patients from each group (i.e. 1.6% and 1.8%, respectively) had surges of testosterone (up to 467 ng/dL and 674 ng/dL, respectively).

Eligard formulation and use

There is no doubt that LHRH agonists have been a significant advance for the treatment of prostate cancer. Several clinical trials have shown LHRH agonists to be as effective as diethylstilbestrol, but avoiding the serious adverse effects of the latter[21]. However, it is clear from the above that not all patients appear to have the same or a consistent response to LHRH agonists.

Eligard (astellas, sanofi-aventis) is a new leuprorelin acetate formulation developed to increase the proportion of patients achieving castrate levels of testosterone and reduce the occurrence of breakthrough responses, without increasing the side effects. It has double the amount of leuprorelin found in other leuprorelin-based products and is available in two doses: 7.5 mg (0.25 mL) and 22.5 mg (0.375 mL) leuprorelin, for subcutaneous injection every 1 and 3 months, respectively. The product is dispended as two syringes and needs to be stored in a refrigerator and allowed to return to room temperature prior to mixing. The product can be stored unmixed at room temperature for up to 2 weeks prior to use[22,23]. Eligard requires a few minutes to prepare as the contents of the syringes need to be mixed thoroughly before use.

The consistent delivery of these high doses over a prolonged period of time is made possible by the use of a novel delivery system, Atrigel (QLT USA, Inc., Fort Collins, CO). This is a biodegradable polymer of D,L-lactide-co-glycolide dissolved in a biocompatible

carrier (*N*-methyl-2-pyrolidone) to form a liquid gel, which is mixed with leuprorelin prior to use. After injection, it forms a solid single sphere implant *in situ*. This biodegrades to release the drug over a period of time[24]. Other depot formulations of leuprolide use lyophilised microspheres for drug delivery: the single, relatively large sphere formed by Atrigel presents a smaller surface area protecting the leuprorelin acetate from degradation on the surface.

In a phase 1 clinical study including 120 healthy male subjects, Eligard 7.5 mg subcutaneous injection was compared to 7.5 mg intramuscular injection of a leuprolide microsphere formulation. It was shown that the microsphere formulation of leuprolide acetate yielded initially a higher release of leuprolide acetate compared to Eligard. However, after this initial release, Eligard maintained higher levels of leuprolide acetate. As a result, the total area under the curve (AUC) was almost twice as big for Eligard than for the microsphere-delivered leuprolide acetate (479 ± 132.6 vs. 248 ± 65.0 ng h/mL, $p < 0.01$; 90% CI ratio of means = 161:226%). This 1.9-fold increased AUC of Eligard resulted in an additional 14 days of testosterone suppression (49 vs. 35 days) (Figure 1)[25].

Eligard 7.5 mg injection was investigated in an open label, multicentre study involving 120 male patients with prostate cancer (117 completed) over a 6-month period. Injections were repeated at 28-day intervals[26] (Figure 2). There was an initial increase in mean serum leuprorelin concentrations to 25.3 ng/ml at 4–8 h (C_{max}) after injection. The initial increase in luteinising hormone (LH) after the first injection was short-lived, returning to below baseline by day 10 post-injection. Subsequent injections produced smaller responses and, after the third injection, peaks were barely detectable (Figure 2). After the initial increase following each injection, serum concentrations remained relatively constant (0.28–1.67 ng/mL). There was no evidence of accumulation during repeated dosing[26]. Only about 10% of the total AUC was observed after 28 days, which indicates that accumulation after multiple doses at 28-day intervals would be small.

In a similar study using Eligard 22.5 mg at 3-monthly intervals, with 111 male patients with prostate cancer completing 6-month follow-up, the initial increase following Eligard 22.5 mg subcutaneous injection, causes mean serum leuprorelin concentrations to rise to 127 ng/mL at 4.6 h (C_{max}) after injection[27]. After this initial increase following each injection, serum concentrations remained relatively constant at

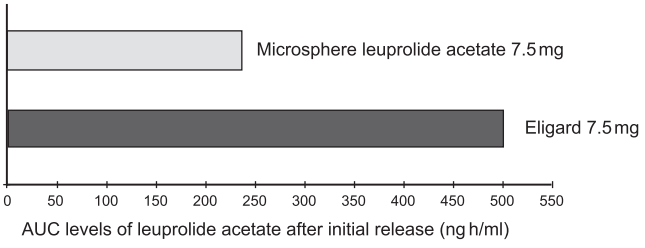

Figure 1. *AUC comparison comparing Eligard 7.5 mg subcutaneous injection with leuprolide acetate microsphere 7.5 mg intramuscular injection*[25]

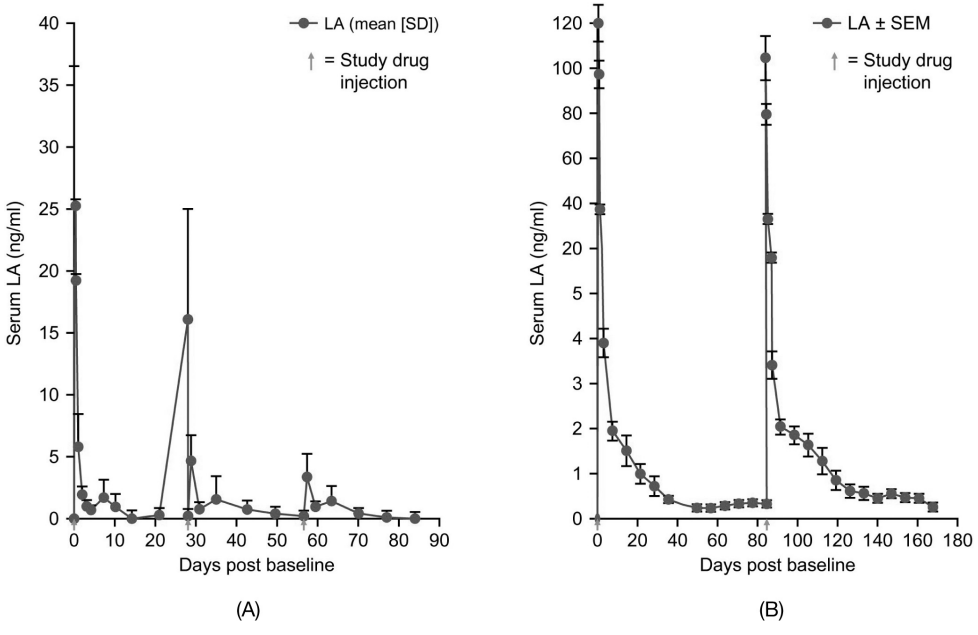

Figure 2. *Serum leuprorelin after administration of (A) Eligard 7.5 mg*[26] *and (B) Eligard 22.5 mg*[27]*. Eligard 7.5 mg was given on days 0, 28 and 56; Eligard 22.5 mg was administered on days 0 and 84. Peak increases in serum leuprorelin were recorded within hours of each injection*

0.2–2 ng/mL (Figure 2). The transient increase in LH declined to below baseline levels by weeks 2–4: after day 28 LH, concentration was extremely low (0.06 mIU/mL). There is no evidence of accumulation during repeated dosing[27].

Eligard and testosterone

Eligard 7.5 mg injection suppressed testosterone to below ≤ 50 ng/dL by day 42 in all patients. By this time point an impressive 98% of patients achieved the bilateral orchidectomy level of ≤ 20 ng/dL. At month 6, mean serum testosterone level was 6.1 ng/dL compared to 361.2 ng/dL at baseline. Furthermore, there were no reports of breakthrough events throughout the study[26].

In the study by Chu *et al.*[27], serum testosterone peaked 2 days after the first injection of Eligard 22.5 mg, and then declined rapidly to castrate levels. By day 35, 100% of patients had achieved testosterone suppression to ≤ 50 ng/dL and remained suppressed for the remainder of the study. Ninety-four per cent of patients achieved testosterone suppression of ≤ 20 ng/dL by the end of the study[27]. At month 6, mean testosterone serum levels were 10.1 ng/dL compared to 367.1 ng/dL at baseline. There was only one patient who had a single testosterone breakthrough (serum testosterone ≥ 50 ng/dL after suppression) on day 49, which was 28 days after suppression. This patient regained and maintained testosterone suppression 14 days after the second injection[27].

Since PSA production and secretion require hormonal influence, androgen deprivation therapy diminishes the ability of benign and malignant prostatic epithelial cells to manufacture PSA. Unless the cancer comprises a critical mass of androgen independent neoplastic cells, serum PSA usually declines significantly and often to undetectable levels. Further increases in serum PSA values despite androgen deprivation therapy indicate progression due to an emerging subpopulation of hormonally resistant clones. PSA levels should decline within the first 6 months after androgen deprivation therapy[28]. PSA concentrations are used as an efficacy measure in clinical trials.

In the study investigating Eligard 7.5 mg injections[26], mean baseline PSA serum concentration was 32.9 ng/mL with only 33.1% of the patients having normal PSA (< 4 ng/mL). At 6 months, serum PSA had declined to a mean concentration of 3.2 ng/mL with 95.7% of patients having a normal PSA serum concentration (Figure 3). PSA also normalized in the study by Chu *et al.*[27].

Eligard safety

The adverse events reported for Eligard are shared with other LHRH agonists. These are expected as a result of the withdrawal of testosterone and include hot flushes, decreased libido, gynaecomastia and tumour flare. A tumour flare response is a result of the transient increase in testosterone levels which occur with LHRH therapy. Normally, these responses are reported in about 10% of patients receiving LHRH monotherapy (that is without concurrent anti-androgen therapy). In both studies with Eligard there were no reports of increased symptoms or flare responses although no anti-androgens were used during the first month of treatment[26,27].

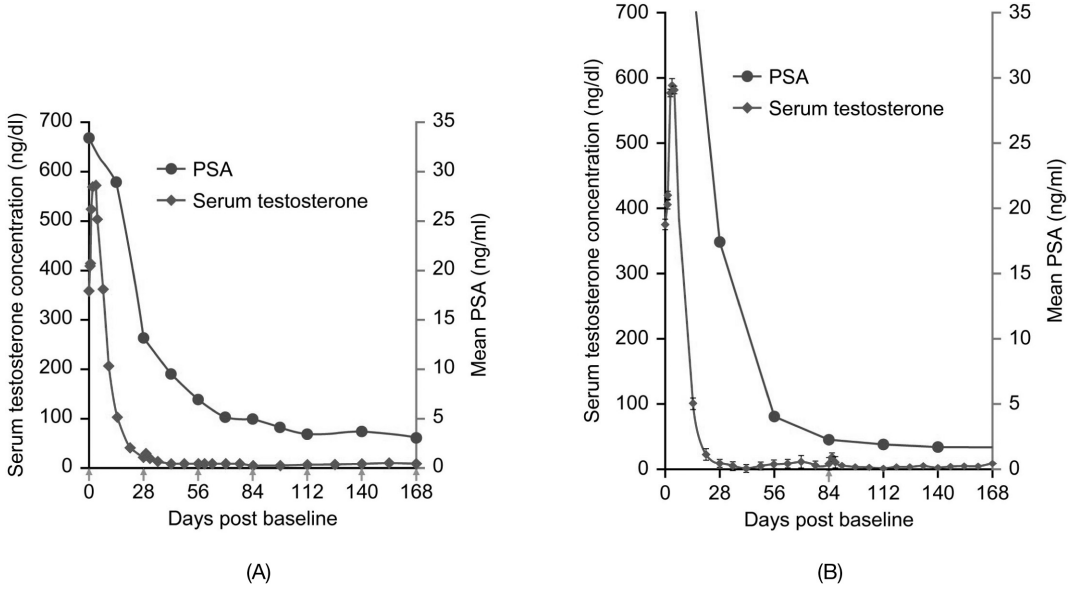

Figure 3. *Serum testosterone and mean PSA concentration using (A) Eligard 7.5 mg[26] and (B) Eligard 22.5 mg injections[27]*

Table 1. Number and percentage of patients experiencing treatment related adverse events[26,27]

Symptom	Eligard 7.5 mg (N = 120)* n(%)			Eligard 22.5 mg (N = 117)† n(%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Hot flushes	53 (44.2)	14 (11.7)	1 (0.8)	57 (48.7)	12 (10.3)	–
Malaise/fatigue	16 (13.3)	5 (4.2)	–	7 (6.0)	–	–
Dizziness/giddiness	4 (3.3)	–	–	4 (3.3)	–	–
Testicular atrophy	5 (4.2)	1 (0.8)	–	2 (1.7)	–	–
Decreased libido	–	–	1 (0.8)	1 (0.9)	–	–
Gynaecomastia	1 (0.8)	1 (0.8)	–	1 (0.9)	–	–

*All other adverse events occurred in two or fewer patients. Gynaecomastia and decreased libido included because of clinical interest

†All other adverse events occurred in three or fewer patients. Gynaecomastia and decreased libido included because of clinical interest

The common adverse events reported for Eligard are summarized in Table 1.

Injection site adverse events were typical of subcutaneous injections, were mild and of brief duration. Mild transient burning following injection was the most common (up to 29%) with no significant difference noted between the two doses[26,27]. The shorter, smaller bore needle compared to that used for other LHRH agonist product is likely to contribute to the relative absence of injection site discomfort. The injection volume for Eligard is small (0.375 mL for Eligard 22.5 mg) compared to other leuprorelin products (2.0 mL of a microsphere formulation containing 11.25 mg leuprorelin acetate for subcutaneous injection). These factors and the route of administration, may make Eligard even more patient friendly.

Conclusion

Prostate cancer is being diagnosed at an early stage, when 5-year survival is excellent with appropriate treatment. In advanced disease, mortality continues to be high. In the majority of cases, suppression of serum testosterone levels is very effective but current LHRH therapy fails to achieve the same degree of testosterone suppression as bilateral orchidectomy, with an estimated 13–34% of patients remaining above the testosterone level of ≤ 20 mg/dL. Although conclusive evidence is not yet available, the consensus among experts is that a target of 20 ng/dL is desirable, with minimal breakthroughs. Both Eligard 7.5 mg and 22.5 mg formulations achieve this target in up to 98% patients. Only one patient, out of 228 patients completing the studies reviewed here had a testosterone breakthrough response, which responded to further injections, and there were no acute-on-chronic episodes with either formulation of Eligard. The side effect profile for Eligard is comparable to other products in this class. The formulation is stable for 2 weeks at room temperature prior to mixing. The small volume is administered subcutaneously via a 20G needle, making Eligard less uncomfortable for the patient compared to the larger volume injections required by other leuprorelin products.

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