

Expert opinion on 6-monthly luteinizing hormone-releasing hormone agonist treatment with the single-sphere depot system for prostate cancer

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INTRODUCTION

The importance of achieving and maintaining effective testosterone suppression is well recognized in the treatment of advanced prostate cancer, with administration of LHRH agonists being the preferred means of achieving this suppression. When first developed, LHRH agonist therapy involved daily s.c. injections, but more recently, 1- and 3-month depot delivery systems have been developed, which have increased the use of these agents, as well as patient compliance [1]. Nevertheless, the possibility of developing formulations that extend the interval between treatment periods to >3 months has also been investigated, to provide patients and physicians with greater flexibility of treatment.

Leuprorelin acetate (LA) is the most widely prescribed depot LHRH agonist, having been used in the treatment of prostate cancer for >20 years [2]. In recent years, a novel formulation of a single-sphere depot of LA (Eligard®, Sanofi Aventis, Bridgewater, CA, USA) has been developed for the treatment of advanced prostate cancer [3,4]. This formulation, which is delivered via the Atrigel® delivery system (QLT Inc., Vancouver, BC, Canada) has been developed to improve the pharmacokinetic profile of LA, producing reliable and sustained suppression of serum testosterone levels in all patients. Eligard has been available as 1- and 3-month formulations delivering 7.5 mg and 22.5 mg of LA, respectively [3,4]. However, a new, extended-release formulation of Eligard was recently developed which delivers 45 mg of the LHRH agonist over a 6-month period [5].

While the efficacy and safety of Eligard 7.5, 22.5 and 45 mg have been well established in

clinical trials, Eligard 45 mg is the first 6-monthly LHRH agonist treatment available for use in prostate cancer; the benefits of this new formulation in the management of advanced prostate cancer needs to be explored [1,6,7]. To discuss the place of 6-monthly Eligard 45 mg in the current treatment of advanced prostate cancer, expert opinion was explored at a Consensus Meeting convened in Paris, France, on 27 January 2007. The panel, which consisted of experts in urology, initially reviewed the clinical data on Eligard 45 mg, and then agreed on several statements designed to assist in achieving consensus on the appropriate use of this new formulation in the treatment of advanced prostate cancer. This report summarizes the clinical experience with Eligard 45 mg and presents the statements developed by the consensus group, along with the evidence used to support each statement.

CLINICAL EXPERIENCE WITH ELIGARD 45 mg

STUDY DETAILS

The efficacy, safety and pharmacokinetics of 6-monthly treatment with Eligard 45 mg were evaluated in a 12-month, open-label, fixed-dose clinical study involving 111 patients with prostate adenocarcinoma (stage >T1, WHO performance score 0–2 and life-expectancy of ≥1 year) [7]. Patients received Eligard 45 mg at 6-month intervals, at baseline and after 168 days. The primary efficacy endpoint was a decrease in serum testosterone to the level accepted as equivalent to that produced by orchidectomy at the time the study was initiated (i.e. ≤ 50 ng/dL on two or more consecutive measurements 1 week apart). For many years,

this level of testosterone was defined as the threshold for testosterone suppression (the 'castrate level'), largely due to the detection limits of old assay techniques [8]. The USA Food and Drug Administration established serum testosterone levels of ≤50 ng/dL as being consistent with levels obtained after surgical castration [9]. However, recent studies using more accurate detection methods have cast doubt on the validity of this threshold, as levels of testosterone have been found to be reduced to a much lower level (15 ng/dL) in men who have undergone bilateral orchidectomy [8]. Indeed, a recent consensus statement has stated that, using orchidectomy as the benchmark, achieving testosterone levels of ≤20 ng/dL after LHRH agonist therapy would be desirable and should be considered the optimal control of testosterone [10]. For this reason, suppression of testosterone to this lower level of ≤20 ng/dL was also assessed in the study evaluating Eligard 45 mg; LH and serum PSA levels were also measured.

PHARMACOKINETICS

In all, 103 patients (93%) enrolled in the Eligard 45 mg study completed the trial and received two injections of the drug. In the pharmacokinetic analysis, injection with Eligard 45 mg was followed by an increase in the mean serum LA concentration to a maximum of 82 ng/mL after the first injection, and 102 ng/mL after the second. Maximum serum concentrations of LA were reached 4–8 h after injection, with concentrations remaining constant thereafter, remaining within the therapeutic range of 0.2–2.0 ng/mL for the remainder of the treatment period [5,7]. The first injection of Eligard 45 mg injection also resulted in an initial rise in LH levels as a result of the

agonist activity of LA; LH levels then declined to below baseline by 7 days, then decreased consistently throughout the first 19 weeks of the study. Importantly, after the second injection of Eligard 45 mg on day 168, there was only a small, transient increase in LH [7].

SERUM TESTOSTERONE LEVELS

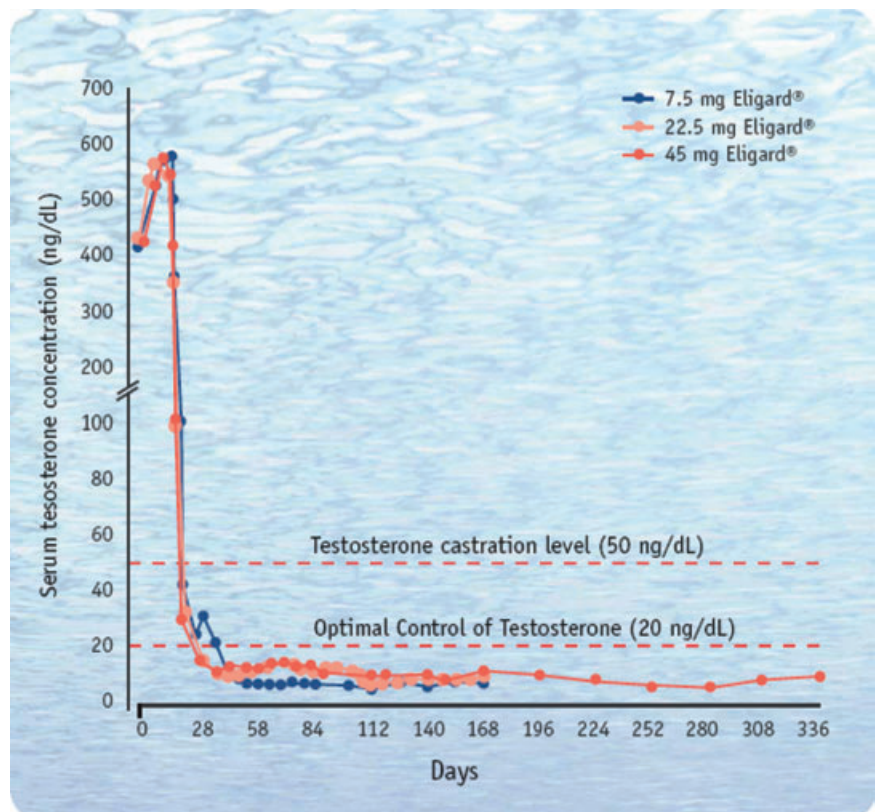
Analysis of serum testosterone levels after injection with Eligard 45 mg showed that patients receiving this new formulation rapidly achieved castrate levels. Administration of the 6-monthly formulation of Eligard produced an initial rise in mean serum testosterone levels, which increased to 588 ng/dL by day 2. However, by day 28, 108/111 patients (97%) had achieved the testosterone castration level of ≤ 50 ng/dL, and 92/111 (83%) achieved the castrate level of ≤ 20 ng/dL, the optimal suppression level, with a mean time to testosterone suppression of 21.2 days (Fig. 1). By the end of the study (12 months), testosterone was below the castrate level (≤ 50 ng/dL) in 102/103 patients (99%) and control of testosterone (≤ 20 ng/dL) was optimal in 91/103 patients (88%). This pattern of testosterone suppression is similar to that observed with the 1-month and 3-month formulations of Eligard (Fig. 1).

In the Eligard 45 mg study, testosterone 'breakthrough' was defined as a serum testosterone level of >50 ng/dL occurring in a patient who had previously achieved castrate suppression of testosterone (i.e. ≤ 50 ng/dL). During the 12-month study, only one incidence of testosterone breakthrough was reported, representing $<1\%$ of the patients who completed the study.

SERUM PSA LEVELS

PSA testing has become the primary method of monitoring patients after treatment for clinically localized prostate cancer [11]. After surgery, an immediate rise in PSA level is correlated with subsequent local recurrence and/or metastasis. Consequently, monitoring PSA levels after therapy is an important part of assessing the effectiveness of treatment. During 12-month treatment with Eligard 45 mg, PSA levels, as might be expected, were found to correlate generally with serum testosterone levels. At baseline, 75.5% of patients were classified as having PSA levels above normal (>4 ng/mL), although PSA levels declined steadily throughout the 12-month treatment with Eligard 45 mg, such that 96%

FIG. 1. Mean serum testosterone levels during 1-, 3- or 6-monthly treatment with Eligard 45, 7.5 or 22.5 mg in clinical trials. Testosterone levels were consistently maintained below the castrate level and the optimal control level throughout treatment with all formulations of Eligard [1,6,7].



of patients had normal levels at the end of the study. Moreover, the proportion of patients achieving normal PSA levels with Eligard 45 mg at the end of the treatment period was similar to that reported for the 1- and 3-month formulation (93% and 96%, respectively) (Table 1).

TOLERABILITY

The tolerability of Eligard 45 mg was shown to be comparable to that with the 1- and 3-month formulations, with mild or moderate hot flushes and fatigue being the most common adverse events with all formulations (Table 2) [1,6,7]. Importantly, there were no reports of severe hot flushes with Eligard 45 mg, and only one patient reported severe hot flushes in clinical trials with the other formulations of the agent (with the 7.5 mg dose) [1,6,7]. There were also no reports of any severe injection site reactions with Eligard 45 mg, with mild and moderate reactions being observed in 14% and $<1\%$ of patients,

respectively. Patients' self-assessment of bone pain, urinary symptoms and urinary pain remained unchanged throughout the 12-month treatment with Eligard 45 mg, and there were no clinically relevant flare reactions to the initial rise in testosterone. Furthermore, no patients receiving Eligard 45 mg discontinued treatment due to adverse events, and there were no clinically significant changes in vital signs. There was no sign of an increase in either the frequency or severity of adverse events with the 6- or 3-month formulations of Eligard when compared with the 1-month formulation [1,6,7].

EXPERT CONSENSUS MEETING

OPTIMAL CONTROL OF TESTOSTERONE WITH ELIGARD 45 mg

Clinical studies with conventional LHRH agonists have shown that 13–34% of patients fail to reach the optimal testosterone level

| Variable | Eligard, mg | | | TABLE 1 Comparative effects of Eligard 45, 7.5 and 22.5 mg on PSA levels in pivotal clinical studies [1,6,7] |
|--|-------------|------|------|--|
| | 45 | 22.5 | 7.5 | |
| Baseline | | | | |
| Mean PSA level, ng/mL | 39.8 | 86.4 | 32.9 | |
| % of patients with normal PSA level (<4 ng/mL) | 25 | 27 | 33 | |
| End of study | | | | |
| Mean PSA level, ng/mL | 1.2 | 1.7 | 3.2 | *Based on testosterone responders. |
| % of patients with normal PSA level (<4 ng/mL) | 96 | 93* | 96 | |

TABLE 2 Treatment-emergent adverse events on treatment with Eligard 45, 7.5 and 22.5 mg. The tolerability of the 6-monthly formulation of Eligard was comparable with that of the 1- and 3-month formulations [1,6,7]

| Adverse event (mild/moderate/severe) % of patients | Eligard, mg | | |
|---|-------------|---------|---------|
| | 45 | 7.5 | 22.5 |
| Hot flushes | 33/24/0 | 44/12/1 | 49/10/0 |
| Fatigue | 7/5/0 | 13/4/0 | 6/0/0 |
| Testicular atrophy | 5/2/0 | 4/1/0 | 2/0/0 |
| Gynaecomastia | 4/0/0 | 1/1/0 | 1/0/0 |
| Injection site reactions | 14/<1/0 | 29/4/<1 | 89/14/0 |

of <20 ng/dL, with 5–17% of patients even failing to reach the historical level of <50 ng/dL, increasing their risk of testosterone breakthrough [8,12–16].

The new 6-month formulation of Eligard is designed to release 45 mg of Eligard over a 6-month period and is the first 6-monthly LHRH agonist treatment available for the treatment of prostate cancer. Clinical trials with Eligard 45 mg showed that this new formulation can provide optimal control of testosterone in patients with prostate cancer throughout the 12-month treatment period [7]. In particular, 83% of patients achieved serum testosterone levels of <20 ng/dL 1 month after their first injection, with 94% of patients achieving this level at 6 months [7]. After 12 months of treatment, 88% of patients treated with Eligard 45 mg achieved testosterone suppression to <20 ng/dL and 99% achieved the historical castration level of <50 ng/dL. Moreover, there was only one incidence of testosterone breakthrough during 12 months of treatment with Eligard 45 mg (<1% of patients) [7].

Considering the data outlined above, the experts agreed on the following statement: 'Eligard 45 mg, the first 6-monthly LHRH

agonist treatment, provides optimal testosterone control in advanced prostate cancer.'

EQUIVALENT EFFICACY OF ELIGARD 45 mg TO THE 1- AND 3-MONTH FORMULATIONS

In addition to the 6-monthly formulation, Eligard 45 mg, Eligard is also available as 1-month (7.5 mg) and 3-monthly (22.5 mg) formulations [3,4]. Studies showed that the profile of LA concentrations after administering Eligard 45 mg is similar to that after the Eligard 7.5 mg and 22.5 mg formulations [1,3–7]. Clinical trials with 1-, 3 or 6-monthly Eligard also showed the efficacy of the three Eligard formulations to be similar. After 6 months of treatment with Eligard 45 mg, 94% of patients had achieved optimal control of testosterone (<20 ng/dL), whereas the proportions of patients achieving this level after Eligard 7.5 mg and 22.5 mg was 97.5% and 94%, respectively [1,6,7]. Furthermore, testosterone breakthrough after Eligard administration was low, regardless of whether the agent was given as a 1-, 3- or 6-monthly formulation (<4% of patients in all studies) [1,6,7]. Six-monthly administration of Eligard also produced similar reductions in serum PSA levels to those produced by the

1- and 3-monthly formulations, with 96%, 93% and 96% of patients, respectively, classified as having normal PSA levels at the end of treatment with Eligard 45 mg, 7.5 mg and 22.5 mg [1,6,7].

These data thus show that the efficacy offered by Eligard, when given either as six 1-monthly injections (Eligard 7.5 mg), or two 3-monthly (Eligard 22.5 mg) injections, are equivalent to those provided by one 6-monthly injection of Eligard 45 mg. In light of this data, the experts agreed to the following statement: 'Eligard® 45 mg provides all the efficacy advantages of six or two injections in a single injection'

FLEXIBILITY FOR THE PHYSICIAN

Complex treatment regimens and high frequencies of dosing can reduce patients' compliance with treatment [17]. Conversely, the use of long-acting formulations has been shown to improve both compliance and treatment outcome in several areas of therapy [18–20]. Sustained-release formulations have also played a role in the acceptance of LHRH agonist therapy in men with prostate cancer. Initially, LHRH agonist treatment required daily s.c. injections; 1- and 3-month depot formulations have now been developed, which have not only contributed to the widespread use of these therapies, but have also increased patient compliance with therapy [3,4].

Early depot systems of LA involved the use of lyophilized microsphere drug-delivery systems [21]. Conversely, the LA in Eligard is delivered by the Atrigel delivery system, which consists of a biodegradable polymer of D,L-lactide-coglycolide dissolved in N-methyl-2-pyrrolidone. After mixing with LA the formulation is injected s.c., where it forms a solid depot that releases the drug over a controlled period, which can be varied by using different formulation variables [22]. Eligard was previously available as 1- and 3-month depot formulations; the recent addition of the 6-monthly formulation gives physicians even greater flexibility of treatment for their patients, allowing optimal testosterone control to be given via 1-, 3- or 6-monthly therapy. Physicians can choose to co-ordinate the monitoring of their patients to coincide with the injections, but the frequency of monitoring does not have to change and, depending on disease stability, this can be agreed with the patient. After discussing the flexibility to physicians

provided by availability of 1-, 3- or 6-monthly formulations of Eligard, the experts were able to agree on the following statement: '*Eligard® is a unique drug offering a full range of depot formulations that provide optimal control of testosterone, using a superior delivery system.*'

In addition to the above statement, the experts also considered that the 6-month formulation of Eligard should be considered to be a convenient and logical option for physicians, as the 6-month period is becoming a standard timing in treating prostate cancer. In particular, prostate cancer trials now routinely evaluate therapies over a 6-month period [23,24]. The experts thus concluded that adding a 6-month formulation of Eligard to the other Eligard formulations is consistent with current medical practice and agreed the following statement: '*A 6-month formulation of Eligard® is logical, as the 6-month period is becoming a standard timing in prostate cancer.*'

CONFIDENCE FOR THE PHYSICIAN

After injection with Eligard via the Atrigel delivery system, the Atrigel/LA mixture forms a solid, spherical s.c. implant, which differs from microsphere-based formulations of LA and other LHRH agonists, as it has a smaller relative surface area, protecting the drug from degradation at the surface of the implant [25]. The efficacy of Eligard, combined with the Atrigel delivery system, thus enables Eligard to provide optimal control of serum testosterone levels over several days or months. With this system, physicians can be confident that Eligard can give consistent delivery of LA when given as either a 1-, 3- or 6-monthly formulation, thereby providing sustained and prolonged control of testosterone [22]. After considering the delivery of Eligard via the Atrigel delivery system, the experts agreed on the following statement: '*Physicians can trust Eligard® to provide patients with sustained and prolonged control of testosterone.*'

CONVENIENCE FOR THE PATIENT

The diagnosis of cancer is clearly devastating for patients and will have a considerable impact on their lives. For this reason, some patients might prefer to be treated with long-acting formulations, as the long periods between dosing might reduce the anxiety

associated with cancer and enable them to continue with their lives. The new 6-monthly formulation of Eligard provides patients with the convenience of a full year of therapy with just two injections, allowing them the freedom to stop worrying about their cancer for up to 6 months.

PSA testing forms an important part of monitoring patients with prostate cancer for disease progression [11]. While the disease status of some patients will require PSA levels to be tested every 3 months, others with stable disease might only need to be seen every 6 months. In patients requiring 6-monthly monitoring, PSA testing can evidently be coordinated with Eligard 45 mg injections, allowing patients 6-month periods with less concern about cancer, to help reduce anxiety and psychological distress. Patients requiring 3-monthly monitoring can also receive Eligard 45 mg, with additional 3-monthly physician visits for PSA testing; alternatively, such patients can receive the 3-monthly formulation of Eligard. The availability of 1-, 3- or 6-monthly formulations of Eligard thus gives physicians greater flexibility, enabling them to tailor management of advanced prostate cancer to the needs of their patients.

The discussion on patient convenience was concluded by the experts agreeing on the following statement: '*Monitoring of patients with advanced prostate cancer can be flexible and tailored to meet the needs of the patient, and does not need to coincide with the LHRH injection.*'

The statements agreed by the experts were:

Flexibility for the physician:

- Eligard 45 mg provides optimal testosterone control in advanced prostate cancer.
- Eligard 45 mg provides all the efficacy advantages of six or two injections in a single injection

Confidence for the physician:

- Eligard is a unique drug offering a full range of depot formulations that provide optimal control of testosterone, using a superior delivery system.
- A 6-month formulation of Eligard is logical, as the 6-month period is becoming a standard timing in prostate cancer.

Convenience for the patient:

- Physicians can trust Eligard to provide patients with sustained and prolonged control of testosterone.
- Monitoring of patients with advanced prostate cancer can be flexible and tailored to meet the needs of the patient and does not need to coincide with the LHRH injection.

CONCLUSIONS

The 1- and 3-month formulations of LHRH agonists like Eligard have been the mainstay of treatment for advanced and metastatic prostate cancer for many years. Recently this new 6-month formulation of Eligard has become available (Eligard 45 mg), raising the possibility of a year of therapy for prostate cancer with only two injections [5]. This new formulation of Eligard has equal efficacy to the 1- and 3-month formulations, providing optimal control of testosterone in almost 90% of patients. After reviewing the clinical data on Eligard 45 mg, members of the expert panel convened to discuss the utility of this new formulation, and agreed that its addition provides a useful option in the management of prostate cancer. Indeed the experts considered that provision of a 6-month formulation of Eligard was a logical step, as the 6-month period is becoming a standard timing in the treatment of prostate cancer. Moreover, use of this extended-release formulation of Eligard might be beneficial for both physicians and patients alike, extending the periods between dosing to enable patients to continue their lives while giving physicians the flexibility to tailor management to their patients' requirements.

CONFLICT OF INTEREST

B.T. is a paid consultant and an investigator for Astellas. All other authors have declared no conflicts of interests.

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Abbreviations: LA, leuprorelin acetate.