COMPARATIVE ANALYSIS OF SIX MONTHS FORMULATION OF LHRH ANALOGUES FOR PROSTATE CANCER TREATMENT

Felipe Herranz Amo


Summary.- OBJECTIVES: To perform comparative analysis of the efficacy and the safety of six months formulation of LHRH analogues indicated for prostate cancer treatment.

METHOD: Search in the PubMed database for clinical trials published between 2006 and 2009 using the following key words: “prostate cancer”, “triptorelin or leuprorelin” and “6-month depot”.

RESULTS: The efficacy of all 3 six months formulation of LHRH analogues currently approved is high (96-98%) for reducing testosterone levels down to below 50 ng/dl.

As the patients included in the three trials are quite heterogeneous, and due to the variability in the way of presenting results, it is not possible to compare testosterone escapes and their effect on PSA levels. The incidence of adverse events (AE) reported across the three trials was high, but only 0.9% to 15.8% were severe. Only one trial reported patient withdrawal (2.5%) because of drug-related AEs.

CONCLUSION: Even though all the studies show and important variability in the analysis and data management, no significant efficacy and safety differences seem to exist.

Keywords: Prostate cancer. LHRH analogue. Six months formulation. Efficacy. Safety.

Resumen.- OBJETIVO: Realizar un análisis comparativo de la eficacia y la seguridad de los análogos de la LHRH de administración semestral con indicación para el tratamiento del cáncer de próstata.

MÉTODO - Búsqueda en la base de datos PubMed de los ensayos clínicos (clinical trials) publicados en el periodo 2006-2009 con las siguientes palabras claves: “prostate cancer” y “triptorelin o leuprorelin” y “6 month depot”.

RESULTADOS – Los 3 análogos de la LHRH de administración semestral autorizados en la actualidad tienen una elevada eficacia (96-98%) en la disminución de los niveles de testosterona por debajo de los 50 ng/dl. Debido a la heterogeneidad de los pacientes incluidos en los 3 ensayos y a la variabilidad en la forma de presentar los resultados, no es posible comparar los “escapes” de testosterona ni su eficacia sobre los niveles de PSA. Se comunicaron una elevada incidencia de acontecimientos adversos (AA) en los 3 estudios, aunque solo fueron graves entre el 0,9% y el 15,8%. Solo en un
INTRODUCTION

Prostate cancer is the most frequent tumour in males and the second cause of cancer death according to the American Cancer Society (ACS) (1) annual estimation.

Ever since PSA measurement generalisation for early detection of prostate cancer, we have been witnesses to the diagnosis tumour stage migration towards localised clinical forms. Namely, in the study about prostate cancer incidence in the Comunidad de Madrid carried out in 2000 (2), 75% of the patients were diagnosed at a localised stage, 12.5% at a locally advanced stage, and the remaining 12.5% had metastases.

Suppression of the circulating testosterone levels is the most widely used palliative treatment for patients with metastatic disease. The European Association of Urology (EAU) (3) clinical practice guideline recommends treating patients with M+ and/or N+ metastatic disease (degree of recommendation: A) with hormones for locally advanced disease (symptomatic patient, PSA > 25-50 ng/ml and PSA-DT < 1 year) or as a radiation therapy adjuvant (degree of recommendation: A), and also for high-risk local disease as a radiation therapy adjuvant and concomitant treatment (degree of recommendation: A). The National Comprehensive Cancer Network (NCCN) (4) clinical practice guideline adds to the above recommendations the hormone treatment for intermediate-risk local disease as both neoadjuvant and concomitant therapy to radiation therapy.

The most frequently applied methods for testosterone suppression are bilateral orchiectomy and the use of LHRH analogues. A population trial performed over the Medicare database between 1993 and 2000 observed increased prevalence of testosterone levels suppression for prostate cancer treatment (from 1.8% to 2.9%, p < 0.001), using LHRH analogues since bilateral orchiectomy went down from 53% in 1999 to 21% in 2000 (5). It is probable that hormone therapy introduction as an adjuvant and concomitant treatment of radiation therapy has considerably increased the current hormone therapy prevalence.

Huggins and Hodges (6) published in 1941 a work on the relationship between orchiectomy and prostate cancer. In 1966 Huggins was awarded the Nobel Prize in Medicine because of his discovery of prostate cancer hormone dependence. In 1971 Schally and Guillemin achieved isolation of the LHRH molecular structure, and in 1973 they synthesised the first LHRH analogue, triptorelin, by substituting an amino acid at position 6 of its structure – this achievement gave them the Nobel Prize in Medicine in 1977. In 1980 Labrie, Coy and Schally used LHRH analogues in prostate cancer patients, and in 1989 the FDA approved the monthly application of these analogues for prostate cancer. Several LHRH analogues have been synthesised ever since.

The elimination half-life of LHRH agonists is short (7), and this is why they started to be administered daily by the subcutaneous or the intranasal routes. Incorporation of the peptide into a bio-compatible and bio-degradable polymer has enabled the administration time to be extended to 1, 2, 3, 4, 6 and 12 months (8), thus facilitating application by the physician and treatment compliance by the patient.

The objective of this trial is to perform comparative analysis of the efficacy and the safety of LHRH analogues six months formulation for prostate cancer treatment.

MATERIAL AND METHOD

Search in the PubMed database for clinical trials published between 2006 and 2009 using the following key words: "prostate cancer", “triptorelin or leuprorelin” and “6-month depot”.

Three clinical trials were found that met the search requirements and the study objective (9-11).

Comparative analysis of the efficacy and the safety of these trials is carried out. The efficacy analysis studies decreased serum testosterone and PSA levels. The safety analysis assesses adverse events.

RESULTS

Types of studies

- The subcutaneous (SC) leuprorelin trial (9) was a 12-month phase III, open-label, multicentre clinical
trial in which one injection was administered every 6 months. The objectives of the study were safety and efficacy.

• The triptorelin trial (11) was a 12-month phase III, open-label, multicentre clinical trial in which one injection was administered every 6 months. The objectives of the study were safety, efficacy and pharmacokinetics [A1].

• The intramuscular (IM) leuprorelin trial (10) was a phase III clinical trial where patients were randomised to receiving one 11.25-mg dose every 3 months, or 22.5 mg every 6 months, or 30 mg every 6 months for 12 months. The primary objectives of this trial were safety and tolerability, and the secondary objective was the analysis of efficacy across all three randomisation arms of the trial.

Sample Size and Inclusion Criteria (Table I)

• The SC leuprorelin trial included 111 patients with a histologic diagnosis of cancer at a stage greater than T1, WHO overall status 0-2 and a life expectancy higher than one year. Only 17% had locally advanced prostate cancer (category C), and 40% presented with metastasis (category D) at the time of diagnosis. The mean PSA at baseline was 39.8 ng/ml (0.19-2.284). Eight patients were withdrawn from the trial, 5 of them due to disease progression.

• The triptorelin trial included 120 patients with either advanced or post-local treatment biochemical recidivation prostate cancer. Of these patients, 51.6% were T3, 17.5% were T4, and 28.3% had biochemical recidivation; only 5% had confirmed metastases. The median PSA at trial baseline was 19.1 ng/ml (0.1-1.630). Five patients were withdrawn from the trial due to disease progression, and 2 of them died.

• The IM leuprorelin trial randomized 120 patients to the 30-mg six months dose, 58 patients to the 11.25-mg quarterly dose, and 118 patients to the 22.5-mg six months dose – the latter patients were not included in the final results of the study report (10). The patients included were suffering from histologically confirmed prostate cancer in any degree and stage that exacted “endocrine castration”, had a life expectancy of greater than one year, and WHO overall status 0-3.

Twenty-one percent of them had received prior treatment with LHRH analogues. No data on tu-

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Objective</th>
<th>Sample size</th>
<th>Inclusion criteria</th>
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<tr>
<td>SC LEUPRORELIN</td>
<td>Phase III, multicentre, open-label</td>
<td>Safety and Efficacy</td>
<td>111 patients</td>
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<td></td>
<td></td>
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<td>• Histologic diagnosis of cancer</td>
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<td>• Stage: higher than T1</td>
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<td>• WHO overall status: 0-2</td>
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<td>• L. E. &gt; 1 year</td>
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<tr>
<td>TRIPTORELIN</td>
<td>Phase III, multicentre, open-label</td>
<td>Safety, Efficacy and Pharmacodynamics [A2]</td>
<td>120 patients</td>
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<td>• Histologic diagnosis of cancer</td>
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<td>• Stage: locally advanced or metastatic</td>
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<td>• E.V. &gt; 18 months</td>
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<tr>
<td>IM LEUPRORELIN</td>
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<td>Safety and Tolerability</td>
<td>296 patients:</td>
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<tr>
<td></td>
<td>- 11.25 mg / 3 months</td>
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<td>- 11.25 mg: 58</td>
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<td>- 22.5 mg / 6 months</td>
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<td>- 22.5 mg: 118</td>
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<td>- 30 mg/ 6 months</td>
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<td>• Any degree and stage</td>
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<td>• WHO overall status: 0-3</td>
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<td>• L.E. &gt; 1 year</td>
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mourn staging are available. Median PSA at baseline was 1.1 ng·ml\(^{-1}\). Seven patients were dropouts: 4 of them died and 3 had severe adverse events.

**Efficacy Analysis (Table II):**

- **SC Leuprorelin:**
  - Ninety-seven percent of the patients achieved castration levels (testosterone < 50 ng/ml) 28 days after treatment initiation. At study completion, 99% of the patients had reached castration levels. No testosterone suppression was observed in 2 patients following drug administration and before being withdrawn from the trial. No information was given on potential testosterone leaks during the trial.
  - At study completion the PSA was higher than 4 ng/ml in 3.9% of the patients, and no changes were seen in the bone pain and voiding symptoms questionnaires; no clinical exacerbation occurred.

- **Triptorelin:**
  - Ninety-seven-point-five percent of the patients showed castration levels (testosterone < 50 ng/ml) 29 days after trial initiation, and 93% maintained such levels throughout the trial. At trial completion, 98.3% kept serum testosterone concentrations at castration levels. Eight patients (6.7%) had testosterone leaks during the trial (2-12 months) – the leak was successfully isolated in five patients, without consequences on serum PSA concentration.
  - Increased PSA concentration with clinical failure was seen in 3 patients (2.5%).

- **IM Leuprorelin:**
  - Ninety-six percent (1.257/1.310) of the testosterone concentrations determined throughout the trial were ≤ 50 ng/dl. Neither the number nor the percentage of patients with testosterone leaks was specified.

  - According to the EORTC response criteria, partial remission was observed at trial completion in 46.6% of the patients, objective stabilisation in 46.6%, and objective progression in 9.2%. The PSA decreased by 89% at study completion.

**Safety Analysis (Table III):**

- **SC Leuprorelin:**
  - The most frequent adverse events were the following: hot flushes (33.3% mild and 24.3% moderate), a reaction at the injection site (14.4% mild and 0.9% moderate), fatigue (7.2% mild and 4.5% moderate), atrophy of the testes (5.4% mild) and gynaecomastia (3.6% mild).

- **Triptorelin:**
  - The most frequent adverse events were the following: hot flushes (71.7%), erectile dysfunction (10%), atrophy of the testes (7.5%), and reaction at the injection site (6.7%).

  Greater local tolerability was observed in the triptorelin trial as compared with the leuprorelin trials (Figure 1).

- **IM Leuprorelin:**
  - Fifteen-point-eight percent of the patients presented with severe adverse events, and 2.5% of them had to be withdrawn from the trial.

  - The most frequent adverse events were the following: hot flushes (34.2%), reaction at the injection site (11.8%), with indurations in 5.8% of the cases, increased sweating (5.8%) and fatigue (1.7%).

**DISCUSSION**

The three clinical trials compared are the pivotal trials submitted for approval to the Regulatory
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Authorities. Efficacy is determined on the base of the percentage of patients who attain the plasma testosterone castration levels exacted by the Authorities on the first month, during the trial and at trial completion (< 50 ng/dl).

Plasma testosterone < 50 ng/dl has been considered the castration reference standard level for over 40 years. More recently some authors recommended that the plasma testosterone level should come as close as possible to the surgical castration level (20 ng/ml) (12,13).

Although the 3 trials show some differences in the fashion they present the plasma testosterone levels (Table II), we may consider that there are no actual differences between them, as the testosterone suppression percentage achieved (< 50 ng/dl) oscillates between 93% and 99%. Independently of being administered monthly or quarterly, the LHRH analogues do not obtain testosterone suppression in all the patients. Between 2% and 12.5% will not obtain testosterone concentrations lower than 50 ng/dl, but between 13% and 46.4% of the patients will not obtain testosterone concentrations lower than 20 ng/dl (14-18).

Testosterone leaks are defined as persistent testosterone elevations to above 50 ng/dl despite continuous administration of LH-RH analogues. According to some authors, such leaks have a clinical meaning and should have therapeutic consequences (19,16). The long-term leak incidence in patients on LHRH analogues varies between 4% and 12.5% (18, 20,21). In a retrospective trial, Morote et al. (22) recently observed the relationship between testosterone leaks and progression-to-androgen-independent-free survival – the greater the leak, the shorter the progression-free survival. Only the triptorelin trial describes in detail the percentage of testosterone leaks and their consequences on PSA. The SC leuprolelina trial masks the number of patients with leaks by analysing in one lot the number of testosterone determinations during the trial, and reporting that 4% of them were higher than 50 ng/dl.

In view of the heterogeneity of the patients included in all 3 trials, and of the variability of presentation of the PSA levels at trial completion, it is not possible to know whether there are differences in this connection.

The adverse effects of the LHRH analogue treatment are a result of the elicited hypogonadism. Hot flushes, anaemia, fatigue, diminished libido, decreased bone density, increased body fat and reduced muscular mass are observed both in the short- and the medium-term. Increased risk of diabetes and

<table>
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<th>Hot flushes</th>
<th>Local reaction</th>
<th>Fatigue</th>
<th>Test. atrophy</th>
<th>Gynecomasty</th>
<th>Erectile Dysfunction</th>
<th>Increased sweating</th>
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<tbody>
<tr>
<td>SC LEUPRORELINA</td>
<td>57,6%</td>
<td>15,3%</td>
<td>11,7%</td>
<td>5,4%</td>
<td>3,6%</td>
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<tr>
<td>TRIPTORELIN</td>
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<td>7,5%</td>
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<tr>
<td>IM LEUPRORELIN</td>
<td>34,2%</td>
<td>11,8%</td>
<td>1,7%</td>
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<td>–</td>
<td>–</td>
<td>5,8%</td>
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![FIGURE 1. Comparative analysis of the local tolerability of LHRH analogues six months administration. Percentage of adverse reactions at the injection site.](image-url)
cardiovascular diseases has been described in the longer-term (23).

The 3 trials reported a high rate of adverse events, most of them mild in nature. There were no withdrawals from the triptorelin and the SC leuprolin trials because of severe adverse events (SAE), whereas 2.5% of the patients in the IM leuprolin trial were withdrawn due to SAEs.

Notwithstanding the fact that there is a significant variability in the analysis and in the way of submitting the data in all 3 trials, no significant differences seem to exist regarding efficacy and safety. The only way of detecting any differences between trials, if any, is to perform a randomised trial comparing these 3 active principles.

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REFERENCES AND RECOMMENDED READINGS
(*of special interest, **of outstanding interest)


