EDITORIAL

Gonadotrophin releasing hormone analogues in prostatic cancer: Can we consider them truly equivalent?☆

Análogos de la hormona liberadora de gonadotropinas en cáncer de próstata: ¿podemos considerarlos en realidad equivalentes?

Prostate cancer, with an estimated 899,000 cases per year worldwide,1 is one of the major health problems in the male population. In Spain, more than 25,000 cases are diagnosed annually (age-standardized incidence of 57.2 per 100,000 inhabitants, similar to that of other developed countries), representing one in 5 tumours among men (21%). With a total of 258,000 deaths in 2008, it is the third leading cause of cancer death in our country and in Europe. In our country, we experienced from 1981 a gradual increase in the rate of prostate cancer mortality until 1998, which reached 24.48 deaths per 100,000 inhabitants, to later evidence a widespread decrease, reaching in 2010 a rate of 17.25/100,000 inhabitants (Fig. 1).2 The latest data published by regions reflect some geographical differences in the risk of death from prostate cancer without a clearly defined pattern, with the highest value in the Principality of Asturias (21.32 per 100,000 inhabitants) and the lowest in Navarra (12.65 per 100,000 inhabitants) (Fig. 2).2

Although certain factors have been identified that have a relationship with prostate cancer (race, inheritance, old age, androgen levels, high-fat diets), early diagnosis has contributed to change the incidence rates in recent years,3 although the downside is that there is increasing scientific evidence that links screening using prostate-specific antigen (PSA) to a diagnosis and supratreatment of prostate cancer. The clinical stage of the tumour is an inadequate method for deciding the most appropriate therapeutic intervention, to be assessed in conjunction with other risk factors: PSA level and Gleason score.4–9

The current possibilities of treatment in prostate cancer include surgery (radical prostatectomy), radiation therapy (external and/or brachytherapy), and hormone therapy (HT). The latter, due to its reversible suppression and androgen ablation ability, can also be combined with a local treatment (prostatectomy or radiotherapy) before the main treatment (neoadjuvant HT), simultaneously (concomitant HT) or after it (adjuvant HT).10

Currently, there is consensus as to the therapeutic usefulness of the HT with gonadotropin releasing hormone (GnRH) analogues in the treatment of high-risk clinically localized cancer (stages I–II), and locally advanced cancer (stage III). They can be used both in neoadjuvant and adjuvant with radiotherapy and in adjuvance after nodal spread surgery. In patients with disseminated prostate cancer (stage IV), GnRH analogues represent the first-choice treatment along with surgical castration.10

All GnRH analogues act through activation of the pituitary GnRH receptors, which steadily cause a pituitary receptor desensitization that brings about a chemical hypophysectomy, thereby blocking the secretion in the pituitary gland of gonadotropins FSH and LH, triggering a chemical castration by cessation of gonadal production of testosterone.

In Spain, the following active ingredients are currently approved: triptorelin (as an intramuscular injection, or as pre-filled syringe for intramuscular or subcutaneous injection), leuprolin (intramuscular injection or as a pre-filled syringe for subcutaneous injection) and goserelin (subcutaneous implantation) in monthly formulation and quarterly formulation. Triptorelin and leuprolin are also in six-monthly formulation. Table 1 summarizes the main characteristics of the GnRH analogues available in Spain.

In order to evaluate the available evidence regarding the effectiveness of GnRH analogues in the treatment of prostate cancer, a literature search was carried out (Pubmed-Medline) in January 2013 with the following terms:

prostate cancer, GnRH, luteinizing hormone releasing hormone, GnRH agonist, and gonadotropin releasing hormone agonist. It summarizes the results derived from compared or meta-analysis clinical trials, in order to obtain the highest possible level of scientific evidence.

We found 3 clinical trials comparing a GnRH analogue to diethylstilbestrol,\textsuperscript{11} orchiectomy,\textsuperscript{12} or surgical castration\textsuperscript{13}; 3 clinical trials that directly compared various analogues with each other in monthly formulation\textsuperscript{14-16}: 3 clinical trials in six-monthly formulation that did not directly compare analogues with each other,\textsuperscript{17-19} a meta-analysis,\textsuperscript{20} and a systematic review updated in 2010.\textsuperscript{21} Previous additional reviews have been discarded that are included in the last 2 references.

The clinical trials that did not directly compare GnRH analogues with each other, with an accumulated experience of 554 patients in monthly treatment and 1720 in six-monthly formulation, concluded that there was no statistically significant difference in the active ingredients studied (leuprolide, goserelin, and buserelin in monthly formulation; triptorelin and leuprolide in six-monthly formulation) in the percentage of patients with objective response (plasma testosterone <50 ng/dl, standard reference level of castration).

![Figure 1](image_url)  
**Figure 1** Evolution of the rate of age-adjusted mortality from prostate cancer in Spain.  

![Figure 2](image_url)  
**Figure 2** Age-adjusted mortality rate from prostate cancer in 2010 in Spain by autonomous communities (national rate: 17.25/100,000 inhabitants).  
Table 1  Main characteristics of the GnRH analogues available in Spain.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Triptorelin</th>
<th>Leuprorelin</th>
<th>Goserelin</th>
<th>Buserelin</th>
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<tbody>
<tr>
<td><strong>Monthly formulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product</td>
<td>Monthly 3.75 mg Gonapeptyl® depot</td>
<td>Monthly 7.5 mg Eligard® depot</td>
<td>Monthly 3.75 mg Ginecrin® depot</td>
<td>Monthly 3.6 mg monthly Zoladex®</td>
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<tr>
<td>Indication</td>
<td>Prostate cancer</td>
<td>Endometriosis</td>
<td>Uterine fibroids</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Preservation</td>
<td>Do not store above 25 °C</td>
<td>Store between 2 °C and 8 °C (refrigerator)</td>
<td>Do not store above 25 °C</td>
<td>It does not require any special storage conditions</td>
</tr>
<tr>
<td>Preparation</td>
<td>Simple and standard reconstitution process</td>
<td>Relatively complex and specific reconstitution process (at least 60 times)</td>
<td>Simple and standard reconstitution process</td>
<td>Not applicable (implantation)</td>
</tr>
<tr>
<td>LRP%</td>
<td>106.99 €</td>
<td>109.28 €</td>
<td>107.09 €</td>
<td>68.10 €</td>
</tr>
<tr>
<td>LRP/month % LRP vs. Decapeptyl®</td>
<td>106.99 € +4.38</td>
<td>109.28 € +2.14</td>
<td>107.09 € +0.09</td>
<td>-41.96</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Active substance</th>
<th>Triptorelin</th>
<th>Leuprorelin</th>
<th>Goserelin</th>
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<tr>
<td><strong>Quarterly formulation</strong></td>
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<tr>
<td>Product</td>
<td>11.25 mg quarterly Eligard® depot</td>
<td>11.25 mg quarterly Procrin® depot</td>
<td>10.8 mg quarterly Zoladex® depot</td>
</tr>
<tr>
<td>Indication</td>
<td>Prostate cancer</td>
<td>Store between 2 °C and 8 °C (refrigerator)</td>
<td>Prostate cancer</td>
</tr>
<tr>
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<td>Do not store above 25 °C</td>
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<tr>
<td>Preparation</td>
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<td>Relatively complex and specific reconstitution process (at least 60 times)</td>
<td>It does not apply (implantation)</td>
</tr>
<tr>
<td>LRP%</td>
<td>274.56 €</td>
<td>282.85 €</td>
<td>315.37 €</td>
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<td>LRP/month % LRP vs. Decapeptyl®</td>
<td>91.52 € +5.16</td>
<td>94.28 € +3.02</td>
<td>105.12 € +14.86</td>
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</table>
The clinical trials directly comparing various GnRH analogues with each other identified certain significant findings, which point to an efficacy and safety profile statistically different in certain objectives analyzed in the 411 patients studied in total in monthly formulation. The work by Heyns et al.,\textsuperscript{15} is the only study that has directly compared 2 analogues (triptorelin and leuprorelin) and was able to identify with a sample of 284 patients (70% of all the patients included in the direct comparisons between analogues) a higher percentage of men with serum testosterone levels <50 ng/dl at 28 days in the leuprorelin group (main variable of the study, with an 8.0% difference and 95% confidence interval between 1.4 and 16.9%). The same study showed a statistically significant difference in a secondary variable, but relevant, as it is the survival rate at 9 months (6.5% difference in favour of triptorelin; \( p = 0.033 \)).

As it has been mentioned, the six-monthly studies did not directly compare analogues with each other, and although the results have certain differences, both in terms of efficacy and safety, the most obvious conclusion to be drawn is that the heterogeneity of the patients included in the 3 studies does not make it possible to draw conclusions beyond the strictly descriptive ones. Some findings suggest that these differences might exist in the six-monthly presentation, since for example the results of the work by Tunn et al.,\textsuperscript{19} included in the fact sheet of six-monthly 30 mg Procrin® powder and solvent for suspension for injection in a pre-filled syringe,\textsuperscript{22} point out that in the group of previously treated patients (up to 3 months) with GnRH analogues, 30 mg six-monthly leuprorelin achieved that 92.9% of the patients did not experience any escape; while in the stratum of na"ive patients, this percentage dropped to 81.5% (11.4% difference). This result is probably the reason why in this formulation there appears in the dosage and method of administration of the fact sheet the recommendation that ‘Six-monthly procrin must be administered only in those patients who have been previously treated with GnRH analogues or LH-RH and/or antiandrogens’, recommendation that is not in another formulation of leuprorelin: 1 mg/0.2 ml procrin injectable vial.\textsuperscript{23} With evidence like this, it is risky to consider equivalent drugs which require, as evidenced by their own fact sheets, different therapeutic history for their indication.

The meta-analysis performed concludes that there is no evidence that shows a difference in effectiveness between GnRH analogues. The systematic review updated in 2010\textsuperscript{21} interprets the results in a more appropriate way, and concludes that the scientific evidence is not sufficient to support an alleged drug class effect among the different analogues in the treatment of prostate carcinoma.

This latter conclusion is more accurate, since the lack of scientific evidence is by no means evidence of something; it is simply lack of evidence. Faced with the usual findings of the positive clinical trials that reject (however unlikely) a null hypothesis of ‘equality’ and accept an alternative hypothesis of ‘difference’ with a fixed a priori error probability (type 1 error), the acceptance as valid of that ‘equality’ null hypothesis requires non-inferiority or bioequivalence designs, which are not those evaluated in this literature review. This conclusion of equivalence, based on the lack of demonstration of superiority, is described as an error in the ICH E9 guideline (Statistical Principles for Clinical Trials – PMP/ICH/363/96)\textsuperscript{24} which in its section 3.3.2 (Trials to show equivalence or non-inferiority) points out that ‘it is inappropriate to conclude equivalence or non-inferiority based on the observation of the non-statistically significant result of a test of the null hypothesis that there is no difference between the researcher product and the active comparator’. Similarly, the guideline warns about the use of the population due to treatment intention in non-inferiority designs (population in which the efficacy and safety results of the phase III clinical trials of superiority are usually analyzed). In its section 5.2.3 (Roles of the Different Analysis Sets), it indicates that ‘there are important aspects in the selection of the analysis populations, since the subjects who drop out of the treatment or control groups tend to have a lack of response, and therefore the results obtained with the analysis of the entire patient sample may be biased
towards demonstrating equivalence. [...] In an equivalence or non-inferiority study, the use of the entire population of patients is not generally conservative and its results must be considered with caution'.

In the same vein, the Food and Drug Administration (FDA) of the United States of America defines that 'two drugs can be considered therapeutically equivalent only if they are pharmacologically equivalent and if they are considered to have the same clinical and safety profile when administered to patients under the conditions specified in their fact sheets'.

The same agency defines that 'two drugs can be considered pharmaceutically equivalent if the following 3 criteria are met: (a) they contain the same active ingredients; (b) they have the same presentation and route of administration; and (c) they are identical in power or concentration'.

The mentioned review by Vilar-Gonzalez et al., 2010 indicates in a similar and more accurate reasoning that: 'there are no studies that attempt to answer the question of the class effect among the analogues or agonists of the luteinizing hormone-releasing hormone. (b) There are indeed reviews and meta-analyses in matters on the therapeutic management with analogues, alone or in combination with surgery and radiotherapy. (c) Direct comparisons do not make it possible to draw definitive conclusions. (d) Indirect evidence is extracted from randomized trials that compare the different analogues to other treatments to obtain androgen deprivation. (e) Other factors related to the pharmacokinetics and pharmacodynamics that may support or reject the existence of the class effect are also assessed'. He concludes, as previously stated, that 'the scientific evidence is not enough evidence to support a putative pharmacological class effect among the different analogues in the treatment of prostate carcinoma'.

In conclusion, the current scientific evidence on the use of GnRH analogues in prostate cancer treatment confirms its therapeutic usefulness as a reversible method to induce androgen suppression or ablation; however, the lack of scientific evidence does not allow us to conclude a putative pharmacological class effect among the various drugs available on the market.

Conflict of interest

The author declares that he has no conflict of interest.

References

21. Vilar-Gonzalez S, Maldonado-Pijuan X, Andres-Garcia I. Dos the pharmacological class effect between the different luteinizing hormone releasing hormone analogues used in the treatment
of prostate cancer have to be assumed? Actas Urol Esp. 2010;34:749-57.


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