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ORIGINAL PAPER

Two different formulations with equivalent effect? Comparison of serum estradiol suppression with monthly goserelin and trimonthly leuprolide in breast cancer patients

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Abstract Data comparing the efficacy of monthly and trimonthly formulations of LHRH agonists are lacking. The aim of this study was to compare the effects of monthly goserelin and trimonthly leuprolide on estradiol levels. A total of 79 early breast cancer patients receiving LHRH agonists for at least 6 months were enrolled in the study. Serum estradiol, FSH and LH levels were measured before drug injection and at the one-month follow-up visit. Thirty-eight patients were treated with goserelin, and 41 patients were treated with leuprolide. Patient characteristics and histopathological variables did not differ between the groups. A comparison of the mean hormone levels between the two groups revealed no significant differences in FSH or estradiol levels ($p = 0.143$ and $p = 0.683$, respectively), but the median LH level was higher in the leuprolide group ($p = 0.025$). Among the patients who did not receive chemotherapy, LH levels were higher in the leuprolide arm ($p = 0.028$). Additionally, FSH levels were significantly higher in the patients over 40 years old ($p = 0.02$) and in those with tumours harbouring cERB-B2 receptor ($p = 0.05$) in the leuprolide group. Three patients (7.9 %) in the goserelin and five patients (12.2 %) in the leuprolide group failed to achieve postmenopausal estradiol levels ($p = 0.707$). The effects of monthly goserelin and trimonthly leuprolide on estradiol levels did not differ significantly. Further research is required to interpret the variable effects on gonadotropins in each subgroup and the relationship between LHRH agonists and survival.

Keywords Breast cancer · LHRH agonist · Premenopause · Estradiol

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Introduction

Breast cancer is a major cause of morbidity and mortality. Approximately 20 % of women diagnosed with breast cancer eventually die of the disease. However, adjuvant chemotherapy and endocrine therapy have major impact on the disease-free and overall survival rates of early breast cancer patients [1, 2]. The probability of developing breast cancer before the age of 40 is nearly 1 in 200, and more than half of the premenopausal women who develop breast cancer have hormone-sensitive disease, termed 'oestrogen receptor-positive', or ER(+) disease [3]. In premenopausal women with ER(+) early breast cancer, optimal adjuvant endocrine therapy includes antiestrogen therapy and ovarian ablation either with surgery, radiotherapy or luteinizing hormone releasing hormone (LHRH) agonists [4].

Luteinizing hormone releasing hormone agonists constitute an effective alternative to irreversible ovarian ablation therapy by inducing a menopausal status that is usually reversible after the cessation of treatment. These agents act by continuous stimulation of the pituitary gland, resulting in a 'desensitization' to gonadotropin secretion and/or a down-regulation of the hypothalamic–pituitary–gonadal axis [5]. Administration of LHRH analogues triggers an initial increase in luteinizing hormone (LH) and estradiol. This increase is eventually followed by a decrease in serum LH levels and a suppression of estradiol to within the menopausal range after approximately 3 weeks of treatment [6]. Several clinical trials have demonstrated the efficacy of LHRH analogues, particularly goserelin, in the management of advanced breast cancer in premenopausal women [7]. Moreover, trials comparing cyclophosphamide, methotrexate, and fluorouracil (CMF) with hormone blockage in premenopausal ER(+) patients have revealed that chemotherapy is equivalent to ovarian ablation, tamoxifen alone or a GnRH analogue alone in an adjuvant setting [8].

The inclusion of LHRH agonists as an adjuvant therapy for hormone-sensitive early breast cancer patients will likely lead to a reduction in the risk of recurrence and longer life spans. The LHRH agonist goserelin has been well studied and is given as a 3.6-mg depot subcutaneously every 28 days for 2–3 years. Although long-acting formulations require fewer clinic visits and thus increase patient compliance, only limited information is available on the efficacies of these agonists [9, 10]. The aim of this study was to compare the efficiency of different formulations of the two LHRH analogues: monthly goserelin (3.6 mg) and trimonthly leuprolide acetate (11.25 mg). We attempted to determine the clinical and pathological factors that may contribute to the effects of these agents on different subgroups of patients.

Patients and methods

Seventy-nine ER (+) premenopausal early breast cancer patients were recruited from the outpatient clinics of the Istanbul University Institute of Oncology for this single-centre prospective study. Eligible patients were defined as those with a histologically confirmed diagnosis of breast cancer without distant metastasis who had received LHRH agonists for at least 6 months in combination with 20 mg of daily tamoxifen.

All the patients underwent surgery including mastectomy and breast-conserving surgery, including primary tumour excision, lumpectomy and quadrantectomy. Sentinel lymph node biopsies and/or axillary lymph node dissections were performed for the assessment of axillary lymph node status as deemed necessary by the surgeon. Initial breast cancer staging was identified according to the criteria listed in the Sixth Edition of the American Joint Committee on Cancer (AJCC). The histological types and grades of the primary tumours were assessed using the Nottingham modification of the Bloom-Richardson criteria [11]. Baseline oestrogen receptor (ER) and progesterone receptor (PR) statuses were determined by immunohistochemical (IHC) staining and were considered negative when the percentage of cells staining positive was less than 1 %. In the case of double-positive staining by IHC, HER2 gene amplification was analysed by fluorescent in situ hybridization (FISH).

After appropriate staging, eligible patients received anthracycline-based chemotherapy alone or in combination with taxanes (paclitaxel or docetaxel). Postoperative radiotherapy was administered to the patients who had undergone breast-conserving surgery and to those with locally advanced disease. All the patients received tamoxifen and LHRH analogues 3 weeks after the completion of systemic chemotherapy or initially as an adjuvant hormone therapy. The patients were treated with either a trimonthly formulation of leuprolide acetate (11.25 mg) or a monthly formulation of goserelin acetate (3.6 mg). The patients who did not fulfil the criteria for menopause were categorized as premenopausal. Menopause was defined as amenorrhoea for 12 or more months in the absence of chemotherapy, tamoxifen or ovarian suppression and FSH and estradiol levels within the postmenopausal range [12].

Patients with any evidence of metastatic disease or a history of secondary malignancy were excluded from the study. Further exclusion criteria were impaired renal and/or liver function tests, abnormal blood cell counts and prior LHRH analogue usage in the neoadjuvant setting or concomitant with chemotherapy. The study methodology was approved by the Institutional Review Board, and all the

patients provided written informed consent before entering the study.

Blood sample collection and assessment

The patients were admitted for hormone screening after at least 24 weeks of ovarian ablation therapy with LHRH analogues. The FSH, LH and estradiol levels were determined from blood samples taken during the first visit, on day 0 (1 day before the administration of LHRH analogues), and 4 weeks later (the one-month follow-up visit). The FSH and LH concentrations were assessed using a chemiluminescent enzyme immunoassay method, and estradiol (E2) concentrations were determined using a double-antibody radioimmunoassay procedure. Serum concentrations below 30 pg/ml were considered to be postmenopausal. The mean FSH, LH and E2 concentrations were calculated as the arithmetic means of values on the 1st week and at 1 month (with only two measurements, the area under the curve for each hormone was equal to the mean hormone level). The follow-up time was defined as the time elapsed from the date of diagnosis until the date of the last visit or contact with the patient. Because no progression or death was detected during follow-up, a survival analysis was not performed.

Statistical analysis

Categorical data were compared using Fisher's exact and Chi-squared tests. Values of $p < 0.05$ were considered statistically significant. The assessment of relationships, comparisons among the various clinical/pathologic parameters and hormone levels were performed using the Mann–Whitney U and Kruskal–Wallis tests for two and three groups, respectively. The Wilcoxon test was used for the evaluation of the variations in the basal and one-month hormone values within the same LHRH analogue group. To evaluate the effects of each independent variable on gonadotropins and estradiol, a logistic regression analysis (a binary logistic model) was utilized. All the analyses were performed using the SPSS 16.0 software package.

Results

Patient characteristics

Seventy-nine sequential patients who had been receiving an LHRH analogue for at least 6 months as an adjuvant hormone treatment were admitted for hormone-level evaluation. The median follow-up time was 27 months (range: 9–66 months), and none of the patients progressed during the follow-up period. Thirty-eight patients were treated with a monthly formulation of goserelin acetate (3.6 mg), and 41 patients were treated with a trimonthly formulation of leuprolide acetate (11.25 mg); both groups concomitantly received 20 mg of tamoxifen daily. The first patient was admitted into the study in December 2010, and the last patient entered the study in December 2011.

Because the patients were receiving LHRH analogues for at least 24 weeks, they were considered to be in a postmenopausal state. All of the patients experienced amenorrhoea starting on the 12th week of treatment. The median duration of LHRH analogue treatment was 22 months (range: 6–41 months). An analysis of the clinical and pathological variables in both groups revealed no statistically significant differences, thus indicating that the groups were relatively homogeneous and suitable for the comparison of hormone levels (Table 1).

LH, FSH and E2 concentrations

The evaluation of variations between the initial and one-month assessments revealed no significant differences in the LH or estradiol levels between the groups ($p = 0.647$ and $p = 0.154$ for LH; $p = 0.08$ and $p = 0.544$ for estradiol in the goserelin and leuprolide groups, respectively). However, in the leuprolide group, the median FSH level was higher than the initial level at 1 month (2.7 vs. 2.1 mIU/ml, $p = 0.013$) (Table 2).

A comparison of the mean hormone levels between the groups revealed no significant differences in the FSH or estradiol levels ($p = 0.143$, $p = 0.683$, respectively), but the median of mean LH levels was higher in the leuprolide group (0.52 mIU/ml vs. 0.31 mIU/ml, $p = 0.025$); see Table 3; Figs. 1, 2. The effects of the different LHRH analogues in the various patient subgroups with respect to their FSH, LH and estradiol levels were also compared. For the patients who did not receive chemotherapy, LH levels were higher in the leuprolide group (0.51 vs. 0.26 mIU/ml, $p = 0.028$). Additionally, FSH levels were significantly higher in the patients who were greater than 40 years old (2.2 mIU/ml vs. 1.5 mIU/ml, $p = 0.02$) and in those with tumours harbouring the cERB-B2 (+) receptor (15.2 vs. 2.1 mIU/ml, $p = 0.05$) in the leuprolide arm. Additionally, the patients who did not receive taxane in their chemotherapy regimens exhibited significantly higher FSH levels in the leuprolide group than those in the goserelin group (3.1 vs. 1.5 mIU/ml, $p = 0.05$); see Table 4. However, a logistic regression analysis revealed that the type of LHRH agonist and tumour stage had statistically significant effects on LH levels ($p = 0.03$, HR: 0.29, 95 % CI: 0.09–0.9 for goserelin vs. leuprolide, $p = 0.03$, HR: 0.08, 95 % CI: 0.009–0.83 for T1 + T2 vs. T3 + T4, respectively). When a similar analysis was performed for the FSH and estradiol values, none of the variables reached statistical significance (Table 5).

Table 1 Clinical and histopathological characteristics of the patients

Variables	Goserelin ($n = 38$) (%)	Leuprolide ($n = 41$) %	p
Age: median (min–max)	39 (22–53)	40 (28–48)	
< = 40	23 (60.5)	20 (48.7)	0.262
>40	15 (39.5)	21 (41.3)	
Tm size: median (min–max)	2.5 (0.8–10) cm	2.5 (0.9–8)cm	
Tumour stage			
T1 + T2	32 (84.2)	35 (85.3)	0.886
T3 + T4	6 (15.8)	6 (14.7)	
Nodal status			
No	13 (34.2)	13 (31.7)	0.511
N1	12 (31.5)	15 (36.5)	
N2	8 (21.0)	11 (26.9)	
N3	5 (13.3)	2 (4.9)	
Grade			
Grade 1 + 2	16 (42.1)	20 (48.7)	0.638
Grade 3	10 (26.3)	16 (39.1)	
Unknown*	12 (31.5)	5 (12.1)	
Type of surgery			
Breast conserving	25 (65.7)	26 (63.4)	0.68
Mastectomy	13 (34.3)	15 (34.6)	
Histology			
IDC	29 (76.4)	29 (70.7)	0.374
ILC	6 (15.8)	7 (17.1)	
IDC + ILC	3 (7.8)	5 (12.2)	
Progesterone receptor			
(−)	4 (10.5)	1 (2.4)	0.189
(+)	34 (89.6)	40 (97.5)	
cERB-B2			
Negative	29 (76.3)	35 (85.3)	0.390
Positive	9 (23.7)	6 (14.7)	
Chemotherapy			
(−)	5 (13.1)	5 (12.1)	0.862
(+)	33 (86.9)	36 (87.9)	
Taxane			
(−)	8 (24.2)	7 (19.4)	0.805
(+)	25 (75.8)	29 (80.6)	

*missing variables were not included in the analysis

Table 2 Differences in the basal and one-month hormone levels with the LHRH analogues

		LH median (min–max)	FSH median (min–max)	Estradiol median (min–max)
Goserelin	Basal	0.26 (0.06–51.9)	2.3 (0.1–11)	17.9 (5–936.1)
	1st month	0.3 (0.04–32.9)	2.2 (0.4–5.2)	15.4 (1.2–52)
Basal versus 1st month	p	0.647	0.729	0.08
Leuprolide	Basal	0.5 (0–76)	2.7 (0.7–17.1)	16.2 (2.7–700.8)
	1st month	0.4 (0.1–17.2)	2.1 (0.3–26.5)	13.5 (2.1–1029)
Basal versus 1st month	p	0.154	0.013	0.544

In both groups, ≥87.8 % of the patients maintained mean E2 serum concentrations below 30 pg/ml, which is considered postmenopausal. Five patients (12.2 %) in the leuprolide group and three patients (7.9 %) in the goserelin group had mean estradiol concentrations greater than 30 pg/ml ($p = 0.707$).

The effects of the LHRH analogues on the hormone levels in the different patient subgroups were also analysed. The estradiol levels were similar in the leuprolide and goserelin groups when the patients were classified by age, chemotherapy history, taxane regimen and tumour characteristics, such as receptor status, grade, stage and nodal status (Table 6). However, among the patients receiving goserelin, the FSH levels were higher in the patients younger than 40 years of age (2.3 vs. 1.5 mIU/ml, $p = 0.046$). Within the leuprolide group, the patients with cERB-B2(+) tumours exhibited higher FSH levels (2.1 vs. 15.2 mIU/ml, $p = 0.037$), and LH levels were much higher in the patients who did not receive chemotherapy (0.51 vs. 0.17 mIU/ml, $p = 0.01$). Additionally, the patients in the leuprolide group who did not receive taxane had higher LH levels (1.8 vs. 0.48, $p = 0.04$). None of the clinical or pathologic variables, except for age factor, had significant effects on hormone levels in the goserelin group.

Discussion

Oestrogen deprivation by ovarian suppression or ablation in premenopausal women is one of the most effective endocrine treatment options for hormone-sensitive breast cancer. Currently, LHRH agonists offer an appropriate modality to achieve ovarian suppression with the advantage of being reversible. The therapeutic value of adjuvant ovarian function suppression with LHRH agonists was established by the year 2000 update of the Early Breast Cancer Trialists' Collaborative Group, which reported a reduction in the risk of recurrence and death at 15 years [13]. In accordance with these data, LHRH agonists have been tested in various strategies in the adjuvant setting, and the data have since confirmed the previous observations of a favourable response to ovarian suppression [14–16]. The 2011 St. Gallen conference guidelines recommend the use of LHRH agonists in combination with tamoxifen for premenopausal women with high-risk disease and for very young patients with intermediate-risk disease [17]. Monthly goserelin injection is the most commonly advocated regimen for this treatment due to the lack of data comparing different types and formulations of LHRH analogues. Thus, the

Table 3 Comparisons of median of mean hormone levels with the two LHRH analogues

	Goserelin	Leuprolide	*p*
LH	0.31 (0.07–26.2)	0.52 (0.08–20.7)	0.025
FSH	2.1 (0.72–8.05)	2.3 (1.08–37.8)	0.143
Estradiol	17.8 (5–473.8)	15.9 (4–864.9)	0.683

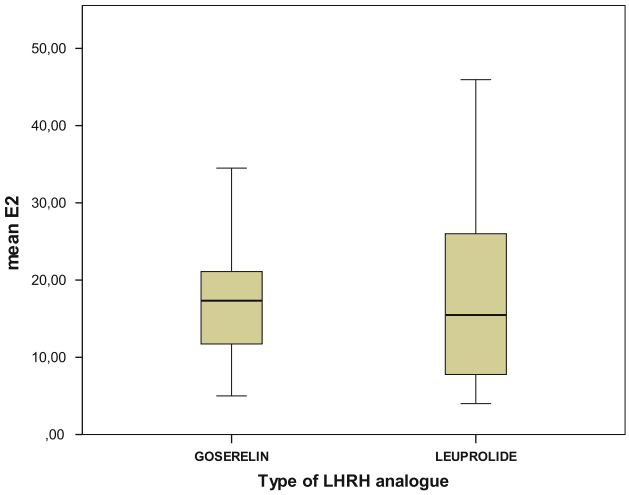

Fig. 2 Mean estradiol levels and 95 % confidence intervals for the LHRH analogues. Values exceeding the 95 % confidence intervals are not shown in the plots

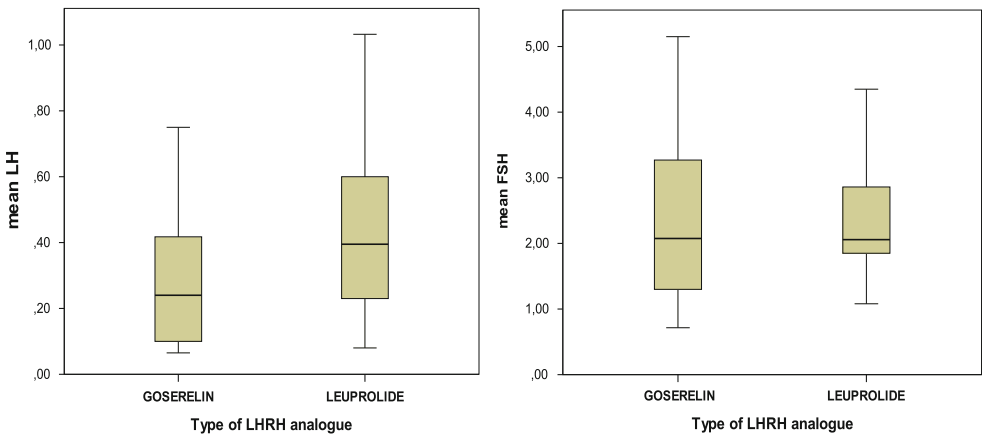

Fig. 1 Mean gonadotropin (LH and FSH) values and 95 % confidence intervals for the goserelin and leuprolide groups. Values exceeding the 95 % confidence intervals are not shown in the plots

Table 4 *p* values for the comparisons of goserelin vs. leuprolide for the different patient subgroups

	LH	FSH	E2
Age ≤ 40	0.127	0.808	1.0
Age > 40	0.27	0.02	0.587
T1 + T2	0.059	0.167	0.966
T3 + T4	0.857	0.556	0.905
Node negative	0.141	0.427	0.657
Node positive	0.301	0.15	0.95
cERB-B2 (−)	0.193	0.249	0.808
(+)	0.218	0.05	0.71
PR (−)	0.8	0.8	0.45
PR (+)	0.092	0.189	0.681
Chemotherapy (−)	0.028	0.127	0.705
Chemotherapy (+)	0.73	0.905	0.556
Cycle of CT > 6	0.035	0.31	0.422
Cycle of CT ≤ 6	0.245	0.308	0.801
Taxane (−)	0.183	0.05	0.945
Taxane (+)	0.076	0.69	0.78

primary objective of this study was to compare the effects of two different formulations of the same class on gonadotropins and estradiol: monthly goserelin and trimonthly leuprolide injections.

Under physiological conditions, LHRH binds to LHRH receptors on the surface of pituitary cells. The administration of LHRH analogues initially causes the occupation of a high proportion of LHRH receptors, leading to a transient increase in serum LH concentration and increased estradiol production by the ovaries [18]. However, continuous administration of LHRH analogues prevents the reappearance of receptors in sufficient numbers to stimulate the secretion of LH and FSH, which is followed by a decline of estradiol levels to postmenopausal concentrations within 3 weeks [19]. Both goserelin and leuprolide are synthetic deca- and nonapeptide analogues of gonadotropin-releasing hormone (GnRH or LHRH) with higher potencies than the natural hormone. Sustained-release formulations containing lactic-glycolic acid copolymer carriers enable the release of these agents over a period of 4 weeks to 3 months depending on the ratio of lactic acid to glycolic acid [20].

This study included patients receiving an LHRH analogue for at least 6 months; hence, the patients were assumed to be in a continuous postmenopausal state at the initial and follow-up assessments. However, 12.2 % of patients in the leuprolide arm and 7.9 % of patients in the goserelin arm did not achieve postmenopausal levels of estradiol. A previous study of serum testosterone levels in metastatic prostate cancer patients receiving goserelin or leuprolide has reported the failure of trimonthly formulations of leuprolide to reach castration levels in 10 % of the patients [21]. In contrast, another study demonstrated the equivalent and sufficient effects of both leuprolide and goserelin for the suppression of serum testosterone levels [22]. In a trial comparing monthly and trimonthly goserelin treatments in breast cancer patients, the proportions of patients achieving postmenopausal estradiol concentrations were similar in both groups: ≥98.8 % of patients had serum E2 concentrations below 30 pg/ml [23]. Accordingly, all the patients experienced amenorrhoea by week 16 in both groups. There are currently no recommendations for the routine biochemical monitoring of breast cancer patients treated with LHRH agonists; however, our study suggests the necessity of assessing hormone levels, as the ratio of patients not achieving postmenopausal status cannot be underestimated in this condition. However, the lack of events due to the short follow-up time of our study prohibits the evaluation of the effect of hormone levels on survival, and further research with long-term follow-up is thus required. Whether estradiol levels during LHRH treatment have prognostic significance in breast cancer, as in prostate cancer, is the subject of another study [24].

In this study, comparing the effects of the LHRH analogues on estradiol levels revealed no significant differences when the patients were analysed according to clinical and histopathological variables. However, the effects on gonadotropins varied when patients were stratified into

Table 5 Logistic regression analysis of the variables influencing hormone levels (above vs. below the median values)

Variables	LH			FSH			Estradiol		
	p	HR	95 % CI	*p*	HR	95 % CI	*P*	HR	95 % CI
Age < 40 vs. > 40 years	0.85	1.11	0.3–3.6	0.68	1.25	0.4–3.8	0.36	1.65	0.5–4.8
T1&T2 versus T3&T4	0.03	0.08	0.009–0.83	0.09	0.22	0.04–1.2	0.51	1.65	0.3–7.3
Node (−) versus node (+)	0.64	1.42	0.3–6.5	0.13	3.34	0.6–16.3	0.37	0.52	0.1–2.2
Chemotherapy (+) vs. (−)	0.37	2.65	0.3–22.5	0.24	3.45	0.4–28.3	0.62	0.60	0.08–4.3
Taxane (+) versus taxane (−)	0.73	0.74	0.1–4.2	0.56	1.64	0.3–8.9	0.63	0.68	0.1–3.2
Goserelin versus leuprolide	0.03	0.29	0.09–0.9	0.91	1.06	0.3–3.0	0.95	1.03	0.3–2.8

HR hazard ratio, *CI* confidence interval

Table 6 Analysis of mean hormone levels according to the clinical and pathological variables among the two LHRH analogues

	Goserelin	Leuprolide	Goserelin	Leuprolide	Goserelin	Leuprolide
Age ≤ 40	0.35 (0.07–16.5)	0.5 (0.1–8.9)	2.3 (0.7–8.0)	2.4 (1.4–27.1)	18 (5–473.8)	17.7 (4–869)
Age > 40	0.22 (0.07–1.6)	0.35 (0.08–1.3)	1.57 (0.85–3.35)	2.2 (1.0–37.8)	16 (7–40.5)	14.4 (4–39.5)
p	0.588	0.505	0.046	0.935	0.932	0.732
T1 + T2	0.26 (0.07–26.2)	0.46 (0.08–8.9)	2.1 (0.8–8.0)	2.3 (1.0–37.8)	17.8 (5–473)	17.7 (14–864)
T3 + T4	0.65 (0.35–1.35)	0.55 (0.44–0.7)	2.7 (2.3–5.1)	2.3 (1.8–9.3)	17.2 (5–26.7)	8.0 (6.3–38.4)
p	0.072	0.531	0.230	0.725	1.0	0.579
Node negative	0.2 (0.07–16.5)	0.4 (0.08–1.03)	1.59 (0.72–4.3)	2.4 (1–37.8)	17.3 (5–39.8)	15 (5–864)
Node positive	0.3 (0.1–2.5)	0.4 (0.1–8.9)	2.2 (0.8–8)	2.1 (1.4–37.5)	18.2 (5–473)	16.8 (4–45.9)
p	0.302	0.549	0.224	0.563	0.888	0.986
Grade 1 + 2	0.24 (0.07–2.5)	0.52 (0.1–2.0)	1.9 (0.8–8)	2.1 (1.4–37.5)	15.7 (5–473)	14.4 (4–45.9)
Grade 3	0.37 (0.1–16.5)	0.46 (0.08–8.9)	2.1 (0.7–4.1)	3.2 (1.0–37.5)	18.5 (7.2–34.5)	26 (4–864)
p	0.698	0.671	0.586	0.373	0.737	0.170
cerBB2 (−)	0.31 (0.07–16.5)	0.4 (0.08–8.9)	1.9 (0.7–8)	2.1 (1–37.8)	17.8 (5.0–473)	17.7 (4–864)
cerBB2 (+)	0.25 (0.07–1.6)	0.6 (0.5–0.7)	2.1 (0.8–3.4)	15.2 (2.5–29.8)	16.8 (7.2–34.5)	15.4 (8–26)
p	0.302	0.399	1.0	0.037	0.986	1.0
PR (−)	0.22 (0.07–16.5)	1.03	2.35 (0.7–4.3)	3.9	15.4 (7–17.3)	5
PR (+)	0.25 (0.7–2.5)	0.4 (0.08–8.9)	2.2 (0.8–8.3)	2.2 (1–37.8)	18.5 (5–473)	16.8 (4–864)
p	0.598	NA*	0.801	NA*	0.255	NA*
Chemotherapy (−)	0.26 (0.07–16.5)	0.51 (0.1–8.9)	1.3 (0.9–3.6)	2.3 (1.4–37.8)	17.5 (7–40)	15.9 (4–864)
Chemotherapy (+)	0.2 (0.07–2.5)	0.17 (0.08–0.3)	2.2 (0.7–8)	1.5 (1.08–4)	17.6 (5–473.8)	15.9 (6.7–32.9)
p	0.449	0.01	0.286	0.160	0.531	0.94
Taxane (−)	0.28 (0.25–2.5)	1.0 (0.6–1.3)	1.5 (0.7–4.3)	3.1 (1.9–37.8)	18.0 (5–473)	15.4 (4–864)
Taxane (+)	0.28 (0.1–16.5)	0.48 (0.1–8.9)	2.3 (0.8–8)	2.2 (1.4–37.5)	17.3 (5–22.2)	15.9 (4–45.9)
p	0.929	0.04	0.161	0.158	0.929	0.981

* Because there was only one patient with a progesterone receptor (−) tumour in the leuprolide group, no comparison was made

subgroups. For individuals older than 40 years and for those who did not receive either chemotherapy or taxane, the suppression of gonadotropins was more evident in the goserelin arm. Additionally, goserelin was more effective for tumours harbouring cerb-B2 receptors, a predictor of the primary resistance to tamoxifen [25]. In addition, a logistic regression analysis supported the independent effect of the type of LHRH agonist on LH levels. However, the analysis of subgroups may be misleading due to the limited number of patients in each group and the unknown clinical consequences of the failure to suppress gonadotropins without a change in estradiol levels.

To the best of our knowledge, this is the first study comparing two different LHRH analogues in different formulations. The limitations of this study include the short follow-up time, which makes the study inadequate for the detection of event-free or overall survival differences between the two agents. The relatively small number of patients in the two groups may have limited the analysis of the effects in the subgroups; however, the current study provides preliminary data to address the issue of safely substituting different LHRH agonists for ovarian suppression in the adjuvant setting.

Conflict of interest The authors declare that they have no conflict of interest and the interventions involved in the study comply with the current laws of Turkey.

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