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Testosterone castration levels in patients with prostate cancer: Is there a difference between GnRH agonist and GnRH antagonist? Primary results of an open-label randomized control study

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Purpose: To compare testosterone castration levels between patients treated with the gonadotropin-releasing hormone (GnRH) antagonist, degarelix, and GnRH agonist.

Materials and Methods: Patients with prostate cancer (PCa) of a single outpatient clinic were randomized (2:1) to receive degarelix (group A) or GnRH agonist (group B). The study evaluated testosterone and prostate-specific antigen (PSA) levels, patients' age, Gleason score and the presence of metastases (nodal or bone). Testosterone and PSA levels were measured at 1st, 6th, 12th, and 18th months. Mann–Whitney test and Spearman correlation were used to investigate independent variable while standard multiple regression was performed to explore statistically significant correlations. Kruskal–Wallis test was used to compare testosterone levels at follow-up.

Results: The study included 168 patients, 107 in group A and 61 in group B. Testosterone levels at 1st month were significantly lower in patients under GnRH antagonist than those receiving GnRH agonist (group A: 22 ng/dL vs. group B: 29 ng/dL, p=0.011). However, PSA values did not differ significantly between groups (group A: 0.130 ng/mL vs. group B: 0.067 ng/mL, p=0.261). In multivariate analysis, treatment with degarelix was an independent factor of lower testosterone levels at 1st month (p=0.013). Comparison of testosterone levels at 6, 12, and 18 months did not reveal any significant difference within each group.

Conclusions: In patients with PCa who are candidates for androgen deprivation therapy, the administration of GnRH antagonist seems to achieve significantly lower testosterone levels compared to treatment with GnRH agonist at 1st month of treatment.

Keywords: Androgen deprivation therapy; Prostate cancer; Testosterone

INTRODUCTION

Prostate cancer is the second leading cause of cancer deaths among men, following lung cancer. The survival rate for prostate cancer is highly favorable, with a five-year survival rate of 98% across all stages. However, this figure drops significantly to 30% in patients who have metastatic prostate cancer. The vast majority of prostate cancer cases

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are diagnosed as either localized disease confined to the prostate or regional disease that has spread to the regional lymph nodes. Only a small percentage of cases, about 6%, have distant metastases [1]. Unfortunately, metastatic prostate cancer is incurable and associated with a significant decrease in quality of life and morbidity [2,3].

Prostate cancer is caused by genetic changes in the cells of the prostate gland, with most tumors being adenocarcinomas. These tumors appear in different areas of the gland and have varying patterns. The disease progresses slowly for many patients and can last for decades. Androgens are essential for the growth of the prostate gland, and androgen deprivation therapy (ADT) is the primary treatment for prostate cancer. Localized prostate cancer can be treated with surgery, radiation, or observation, while metastatic prostate cancer is treated with medical castration using ADT agents. These agents aim to reduce testosterone levels, shrink the tumor, and improve survival and symptoms [4].

Pharmaceutical castration is the cornerstone of treatment for patients with metastatic castrate-resistant prostate cancer. ADT, combined with radiotherapy, is also a recommended treatment option in non-metastatic prostate cancer, significantly improving overall and cancer-specific survival rates [5,6]. As effective modern treatments have evolved, ADT is now used to treat earlier-stage diseases and not only metastatic ones. It is recommended for men receiving 125I-transperineal prostate brachytherapy who require prostate downsizing and also for those undergoing external beam radiotherapy for locally advanced, unfavorable-risk diseases. The main goal of ADT in prostate cancer treatment is to reduce testosterone levels to below castration levels [7-9]. Testosterone levels lower than 50 ng/dL are considered necessary for successful castration. However, bilateral orchiectomy reduces mean testosterone levels to approximately 15 ng/dL [10], and optimal testosterone levels after ADT are estimated to be 20 ng/dL [11]. However, most patients eventually progress despite ADT, with rising prostate-specific antigen (PSA) levels, the development of new metastases, or worsening symptoms, even when testosterone levels are very low [4].

Luteinizing hormone-releasing hormone (LHRH) agonists and LHRH antagonists are both used for ADT and are considered to be equally effective [12]. Degarelix and gonadotropin-releasing hormone (GnRH) agonists are the two most commonly prescribed drugs for ADT in prostate cancer. The pharmacobiological behavior of these drugs differs from each other. The mechanism of action in patients with prostate cancer is based on central hormone suppression, which reduces circulating testosterone levels [13]. LHRH agonists bind and activate LHRH receptors, causing an initial temporary peak in luteinizing hormone (LH) levels. Subsequently, LHRH receptors are downregulated, and LH and testosterone levels decrease [14,15]. In contrast, LHRH antagonists cause an immediate decrease in LH and testosterone levels by directly inhibiting LHRH receptors [14]. The aim of this study is to investigate and compare testosterone levels between LHRH agonists and the LHRH antagonist, degarelix. Secondary outcomes include examining differences in PSA levels between the groups during the castration period.

MATERIALS AND METHODS

This was a single-center, open-label, randomized (ratio for group A:B=2:1) controlled, parallel-group trial. Adults men with histology documented prostate adenocarcinoma receiving ADT from January 1, 2019 onwards were recruited. Patients with metastatic hormone-naive prostate cancer, patients with recurrence of prostate cancer after radical prostatectomy who received ADT before adjuvant radiotherapy and those treated with radiation therapy were included in the study. Exclusion criteria was concomitant chemotherapy or new androgen pathway targeting agents. Patients were randomized (2:1) using simple randomization with Excel into two groups: those treated with degarelix (LHRH antagonist - group A) and those prescribed Leuprolide (LHRH agonist - group B). Degarelix was administered at an initial dose of 240 mg (2 injections of 120 mg) followed by monthly (every 4 wk) doses of 80 mg. Leuprolide was administered at a dose of 11.25 mg at 3-month intervals. Both agents were administered subcutaneously on the abdomen area according to the manufacturer's instructions. Bicalutamide (tablet of 50 mg) could be administered 1 week before initiation of Leuprolide for flare phenomenon protection according to the investigator's judgment. Testosterone and PSA levels were measured in the hospital's laboratory. All participants provided written informed consent according to the principles of the Helsinki Declaration. The study protocol was approved by the Scientific Ethics Committee of Papageorgiou Hospital (IRB no. 743/10-12-2018; Thessaloniki, Greece).

The primary aim of the study was to compare testosterone levels between the two groups. Testosterone levels were measured at the first month of treatment, at 3-month follow-up, at 12-months follow-up and at 18 months follow-up. PSA levels, Gleason score, the presence of nodal and bone metastases during initial diagnosis were recorded and included as variables in multivariate analysis. Percentage of patients achieving castration testosterone levels <50 ng/dL and <20 ng/dL were also evaluated and compared between the groups. Patients with incomplete follow-up were exclud-

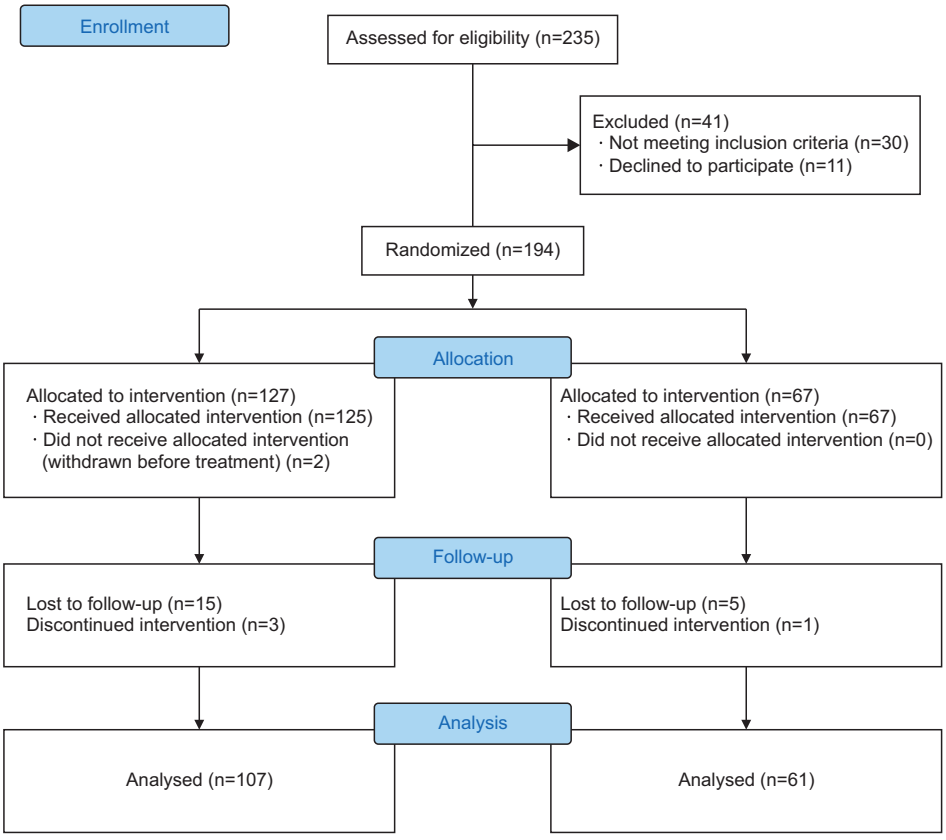

Fig. 1. Patient Consolidated Standards of Reporting Trials flow diagram.

ed from the analysis (Fig. 1).

Data were analyzed using the IBM SPSS, version 27 for Windows (IBM Corp.). Descriptive statistics were estimated for each variable in each group. Kolmogorov–Smirnov was performed in order to examine normality, because the sample in both groups was >50. A p-value <0.05 indicated not normally distributed sample requiring non-parametric tests. Normally distributed variables were presented with mean, standard deviation, and range, while for non-parametric variables, median (Md) and interquartile range (IQR) were used. A t-test was also used for normally distributed variables while Man–Whitney test was used for non-parametric variables. Differences in testosterone levels, PSA levels, Gleason score (Mann–Whitney test), and age (t-test) between the groups were examined. The presence of nodal and bone metastasis and d'Amigo risk stratification between group A and B was also examined (chi-square test).

Furthermore, bivariate analysis with testosterone levels as the dependent variable and each independent variable separately was performed using non-parametric tests (Spearman's correlation, Mann–Whitney test). Multivariate analysis (standard multiple regression) was also performed to reveal independent determinants of testosterone levels in patients undergoing ADT. Statistical significance was set at 0.05, with results less than 0.05 being statistically significant and a confidence interval of 95% in all tests.

RESULTS

A total of 168 participants were included in the study, with 107 in group A (mean age 71.90±7.89 y) and 61 in group B (mean age 70.78±7.05 y, p=0.359, t-test). The two groups did not differ significantly in terms of age, initial PSA value, D'Amico risk stratification, presence of nodal and bone metastasis (Table 1). Testosterone levels at the first month were significantly lower in patients treated with degarelix (group A: Md=22 ng/dL, IQR=14.25 ng/dL; group B: Md=29 ng/dL, IQR=20 ng/dL, p=0.011, Mann–Whitney test). In group A, 96.3% of patients (n=103/107) had testosterone levels ≤50 ng/mL, compared to 88.5% of patients in group B (n=54/61, p=0.100). Similarly, 42.1% of patients in group A (n=45/107) had testosterone levels ≤20 ng/mL, while 29.5% of patients in group B (n=18/61) had testosterone levels ≤20 ng/mL (p=0.150). PSA values did not differ significantly between the groups on the day of testosterone measurement (group A: Md=0.130 ng/mL, IQR=1.560 ng/mL; group B: Md=0.067 ng/mL, IQR=0.465 ng/mL, p=0.261, Mann–Whitney test).

The investigation of the relationship between testosterone levels and each variable in both groups revealed a weak negative correlation between increasing age and testosterone

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Table 1. Demographics and clinical characteristics of patients treated with GnRH antagonist (group A) vs. patients treated with GnRH agonist (group B)

Variable	Group A (n=107)	Group B (n=61)	p-value
Age (y)	71.90±7.89	70.78±7.05	0.359[a]
Initial PSA (ng/mL)	12.5 [33.22]	10 [13.25]	0.091[b]
Gleason score	7 [1]	7 [1]	0.766[b]
Clinical T stage			0.066[c]
cT1–T2a	31 (29.0)	24 (39.3)	
cT2b	33 (30.8)	21 (34.4)	
>cT2b	43 (40.2)	16 (26.2)	
D'Amico risk			0.107[c]
Low	21 (19.6)	18 (29.5)	
Intermediate	29 (27.1)	21 (34.4)	
High	57 (53.3)	22 (36.1)	
Nodes metastasis			0.538[c]
Present (+)	25 (23.4)	11 (18.2)	
Absent (-)	82 (76.6)	50 (81.8)	
Bone metastasis			0.526[c]
Present (+)	21 (19.6)	9 (14.8)	
Absent (-)	86 (80.4)	52 (85.2)	

Values are presented as mean±standard deviation, median [interqurtile range], or number (%).
GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antigen.
[a]:A p-value by t-test.
[b]:A p-value by Mann–Whitney U test.
[c]:A p-value by χ^2 test.

Table 2. Correlation of testosterone levels with examined variables (p-values) in patient with prostate cancer treated with androgen deprivation treatment (n=168)

Variable	Spearman's correlation[a]		Multivariate regression[b]
	Rho's	p-value	p-value
Age at diagnosis	-0.165	0.035	0.067
Initial PSA	-0.032	0.690	
PSA (on the day of testosterone measurement)	0.042	0.585	
Gleason score	0.052	0.513	
Nodes (+)	0.054[c]		
Bone meta (+)	0.425[c]		
Degarelix	0.011[c]		0.013
D'Amigo risk	0.616[d]		

PSA, prostate-specific antigen.
[a]:Spearman's correlation was used because variables were not normally distributed, Rho.
[b]:Standard multiple regression was performed in order to investigate significant variables from previous analysis -left columns (age at diagnosis and treatment with degarelix) and find independent variables.
[c]:Mann–Whitney test.
[d]:Kruskal–Wallis test.

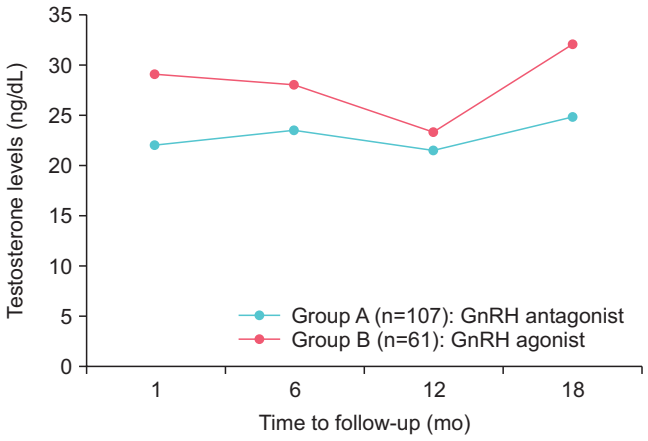

Fig. 2. Testosterone levels of patients treated with gonadotropin-releasing hormone (GnRH) antagonist (group A) vs. patients treated with GnRH agonist (group B). No statistically significant difference in follow-up castration levels within each group (group A: p=0.540, group B: p=0.121, Kruskal–Wallis test) between the 3 time points (6, 12, and 18 months).

levels (rho=-0.165, p=0.035, Spearman's correlation). In addition, treatment with GnRH antagonist was associated with lower testosterone levels (p=0.011, Mann–Whitney test). A further multivariate analysis (standard multiple regression) was performed with testosterone levels as the dependent variable and age at diagnosis, Gleason score, treatment with degarelix, initial PSA, and duration of treatment as independent variables. Treatment with degarelix was negatively and independently related to testosterone levels (p=0.013, B=-10.41 Beta=-0.207), with this model explaining 7.3% of the variance in testosterone levels (Table 2).

Finally, follow-up testosterone levels were examined at three different time points, at 6, 12, and 18 months (Fig. 2). There were no statistically significant differences in castration levels in each group (group A: p=0.540, group B: p=0.121, Kruskal–Wallis test) between the 3 time points (Table 3).

DISCUSSION

In our study, we found that testosterone levels were significantly lower in patients treated with degarelix compared to those prescribed LHRH agonist at the first month of treatment. Furthermore, multivariate analysis revealed that treatment with degarelix resulted in lower testosterone levels at the first month. However, when testosterone levels <20 ng/dL were examined and during follow-up, there was no difference between the groups.

Our results are in accordance with current reviews reporting that patients on degarelix showed a more rapid decline in testosterone and PSA levels initially compared to

Table 3. Testosterone levels per group and time of follow-up

Time of follow-up	Testosterone levels (ng/dL)			p-value[a]
	6 mo	12 mo	18 mo	
Group A (n=107)	23.5 [20.5]	21.54±7.85	24.80±11.68	0.540
Group B (n=61)	28 [19.0]	23.25±10.72	32.00±15.47	0.121

Values are presented as median [interquartile range] or mean±standard deviation.
[a]:A p-value by Kruskal–Wallis test.
Group A: prostate cancer patients treated with LHRH antagonist; Group B: prostate cancer patients treated with LHRH agonist.

those prescribed goserelin. Nonetheless, PSA and testosterone suppression to castrate levels were similar for the remaining period [16]. Bilateral orchiectomy was observed to reach castration levels in less than 12 hours [17], while degarelix achieves testosterone levels <50 ng/mL in more than 90% of patients in 1 to 3 days [18]. On the contrary, LHRH agonists require 2 to 3 weeks for testosterone to reach castration levels [19].

According to a 12-month, comparative, randomized, open-label phase III study in patients with prostate cancer, more than 95% of those prescribed degarelix achieved testosterone levels <50 ng/mL on the 3rd day of treatment. On the other hand, none of the patients treated with leuprolide scored castration levels on the same day after administration. However, after the 28th day and during the first years of observation, the percentage of patients with testosterone levels ≤50 ng/mL in each group did not differ significantly. According to the authors, the faster reduction rate in testosterone levels with the use of degarelix leads to a significantly greater decrease in PSA values, as noted during the 1st month of treatment [20].

In our study, the percentage of patients with testosterone levels ≤50 ng/mL and ≤20 ng/mL after 1 month of treatment did not differ significantly between those prescribed LHRH agonists and those treated with LHRH antagonist. Both the rate at which castration is achieved and the minimum testosterone levels during castration are independent risk factors affecting time to disease progression. Wang et al. [21] associated testosterone levels <25 ng/dL in 1 to 6 months after initiation of treatment with later progression to castrate-resistant prostate cancer. As a result, ADT should aim for both the minimum possible testosterone levels and faster reduction rate, particularly in cases with high testosterone levels before induction of therapy [22].

The clinical impact of attaining castration levels in less than the first month of therapy has not yet been studied and involves avoiding flare-up in patients treated with LHRH agonists. In a study performed by Crawford et al. [23], including patients crossing over from leuprolide to degarelix, PSA progression-free survival hazard rate was significantly decreased for those changing groups while it remained stable for those continuing degarelix treatment. A meta-analysis performed by Hosseini et al. [24] comparing GnRH antagonists with LHRH agonists showed that the former had significantly more effects on PSA and testosterone reduction but only during the first month of the treatment. The same results regarding testosterone were confirmed in another meta-analysis reporting that degarelix produced castration levels in a higher percentage of cases only during the first month [25]. The latest non-inferiority studies reported that degarelix was non-inferior to goserelin in achieving and maintaining testosterone suppression at castrate levels during 1-year treatment, while PSA patient-free survival was significantly higher with degarelix [26]. Similarly, the 3-month formulation of degarelix was non-inferior to goserelin concerning testosterone suppression [27]. However, the former two studies were performed in Chinese and Japanese population exclusively.

The study has several limitations that should be considered. Firstly, it is a single center study and the sample size could have been larger and included more patients in each group. While these are the primary results of the study, further results are expected by the end of the study. Additionally, the inclusion of patients of different stages under ADT and the exclusion of patients with incomplete follow-up may contribute to potential bias. Moreover, it should be noted that while the study found significant differences in testosterone levels between the two treatment groups at the first month, testosterone levels are not directly linked to patients' survival since disease progression was not examined in this study.

CONCLUSIONS

Although our study has some limitations, it suggests that the LHRH antagonist, degarelix, initially achieves lower testosterone levels compared to LHRH agonist in patients with prostate cancer under ADT. However, to draw conclusions on clinical outcomes, such as time to progression to castrate-resistant prostate cancer and cancer-specific survival, multi-

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center long-term observational studies are required.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Vaios-Konstantinos Mytilekas, Efstathios Papaefstathiou, and Periklis Koukourikis. Data acquisition: Vaios-Konstantinos Mytilekas, Efstathios Papaefstathiou, Periklis Koukourikis, Xenofon Ouzounidis, and Stavros Kazantzidis. Statistical analysis: Efstathios Papaefstathiou. Data analysis and interpretation: Vaios-Konstantinos Mytilekas, Efstathios Papaefstathiou, and Periklis Koukourikis. Drafting of the manuscript: Vaios-Konstantinos Mytilekas and Efstathios Papaefstathiou. Critical revision of the manuscript: Periklis Koukourikis and Konstantinos Hatzimouratidis. Administrative, technical, or material support: Periklis Koukourikis and Stavros Kazantzidis. Supervision: Konstantinos Hatzimouratidis. Approval of the final manuscript: all authors.

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