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Authors:

Cui Y, Zong H, Yan H, Li N, and Zhang Y

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Degarelix versus Goserelin plus Bicalutamide Therapy for Lower Urinary Tract Symptom Relief, Prostate Volume Reduction and Quality of Life Improvement in Men with Prostate Cancer: A Systematic Review and Meta-Analysis

Yuanshan Cui Huantao Zong Huilei Yan Nan Li Yong Zhang

Department of Urology, Beijing Tian-Tan Hospital, Capital Medical University, Beijing, China

Key Words
Degarelix · Goserelin · Prostate cancer · Meta-analysis · Randomized controlled trial

Abstract
Objective: We performed a systematic review and meta-analysis to assess the efficacy and tolerability of degarelix for lower urinary tract symptom relief, prostate volume reduction and quality of life improvement in men with prostate cancer (PCa). ***Materials and Methods:*** A literature review was performed to identify all of the published randomized controlled trials (RCTs) that used degarelix versus gonadotropin-releasing hormone agonists plus antiandrogens therapy for the treatment of PCa. The search included the following databases: MEDLINE, EMBASE and the Cochrane Controlled Trials Register. ***Results:*** Three publications involving a total of 466 patients were used in the analysis, including three RCTs that compared degarelix with goserelin plus bicalutamide therapy for PCa over 12 weeks. For the comparison of degarelix with goserelin plus bicalutamide therapy, International Prostate Symptom Score (IPSS) reduction (standardized mean difference [SMD] = –1.85, 95% confidence interval [CI] = –2.97 to –0.72, p = 0.001) and IPSS ≥13 (SMD = –2.68, 95% CI = –4.57 to –0.78, p = 0.006) indicated that decreases in IPSS were greater in degarelix-treated patients than in goserelin plus bicalutamide-treated patients. ***Conclusions:*** Our meta-analysis indicates that, compared with goserelin plus bicalutamide, degarelix has significantly more pronounced effects on lower urinary tract symptoms.

Introduction

Since Huggins and Hodges [1] demonstrated that surgical castration resulted in significant clinical improvement in men with advanced prostate cancer (PCa), androgen deprivation therapy (ADT) has been the mainstay for management of advanced/metastatic PCa [2]. ADT is also recommended in combination with radiotherapy for the management of intermediate and high-risk localized disease [3].

Surgical castration, the seminal 'gold standard' ADT, is irreversible and can have negative psychological effects on patients [4]. It has generally been replaced by medical castration induced by gonadotropin-releasing hormone (GnRH) agonists [5]. The agonists initially stimulate pituitary GnRH receptors, resulting in the rapid release of gonadotropins and testosterone (surge), which delays the

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Yong Zhang
Department of Urology, Beijing Tian-Tan Hospital
Capital Medical University
No. 6 Tiantan Xi Li, Dongcheng District, Beijing 100050 (China)
E-Mail doctorzhy@126.com

onset of androgen deprivation and has been associated with triggering rare clinical complications, such as bladder outlet obstruction and increased pain or spinal cord compression in metastatic patients [6]. To avoid such complications, GnRH agonists in high-risk patients have to be co-administered with an antiandrogen to block the effects at the testosterone receptor level [7].

Degarelix, a new GnRH receptor blocker (antagonist), has been developed as a novel therapy for patients with PCa who need ADT. Degarelix binds to and blocks the GnRH receptors in the anterior pituitary gland, resulting in a decreased secretion of both luteinizing hormone and follicle-stimulating hormone. This leads directly to a rapid decrease in the production of testosterone. Clinical trials have demonstrated that degarelix can offer improved disease control when compared with a GnRH agonist in terms of superior PSA progression-free survival and a more significant impact on bone serum alkaline phosphatase and follicle-stimulating hormone.

GnRH agonists (plus antiandrogen flare protection) are also the standard treatment for patients with PCa suffering from lower urinary tract symptoms (LUTS). The aim of the present study was to perform a meta-analysis to clarify the effect of degarelix versus goserelin plus bicalutamide on total prostate volume (TPV) reduction, International Prostate Symptom Score (IPSS) improvement and changes in the quality of life (QoL) in men with PCa.

Materials and Methods

Search Strategy

MEDLINE (from 1966 to December 2013), EMBASE (from 1974 to December 2013), the Cochrane Controlled Trials Register and the reference lists of the retrieved studies were searched to identify RCTs that referred to the effect of degarelix on PCa. The search terms used included 'degarelix', 'prostate cancer' and 'randomized controlled trials'.

Inclusion Criteria

Randomized controlled trials (RCTs) were included if they met the following criteria: (1) the study design included treatments with degarelix; (2) the study provided accurate data that could be analyzed, including the total number of subjects and the index values, including IPSS, TPV and QoL; (3) the full text of the study could be accessed.

Trial Selection

When the same RCT study was published in various journals or in different years, the most recent publication was used for the meta-analysis. Each study was included if the same group of researchers studied a group of subjects with multiple experiments. The authors of the present paper discussed each of the RCTs that were included and excluded studies that either failed to meet the inclusion criteria or could not be agreed upon. A flow diagram of the study selection process is presented in figure 1.

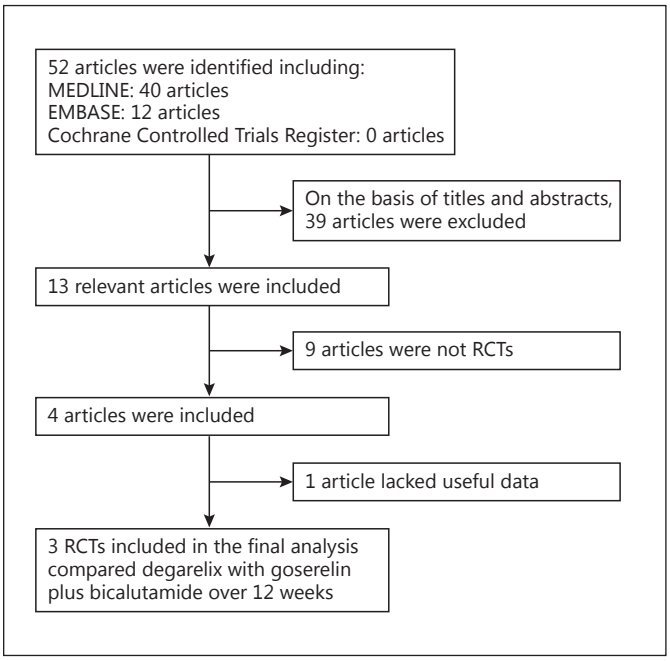

Fig. 1. Flow diagram of the study selection process.

Quality Assessment

The quality of all of the retrieved RCTs was assessed using the Jadad score [8]. All of the identified RCTs were included in the meta-analysis, regardless of the quality score. The methodological quality of each study was assessed according to how patients were allocated to the arms of the study, the concealment of allocation procedures, blinding and data loss due to attrition. The studies were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. Based on the quality assessment criteria, each study was rated and assigned to one of the three following quality categories: (A) if all of the quality criteria were adequately met, the study was deemed to have a low risk of bias; (B) if one or more of the quality criteria were only partially met or were unclear, the study was deemed to have a moderate risk of bias; (C) if one or more of the criteria were not met or were not included, the study was deemed to have a high risk of bias. Sensitivity analyses were then performed on the basis of whether these quality factors were adequate, inadequate or unclear. Differences were resolved by discussion among the authors.

Data Extraction

The information from the databases that was collected included the following: (1) the name of the first author and the publication year, (2) the study design and sample size, (3) the therapy that the patients received, (4) the country of the patients, and (5) the data, including the changes in TPV, IPSS and QoL.

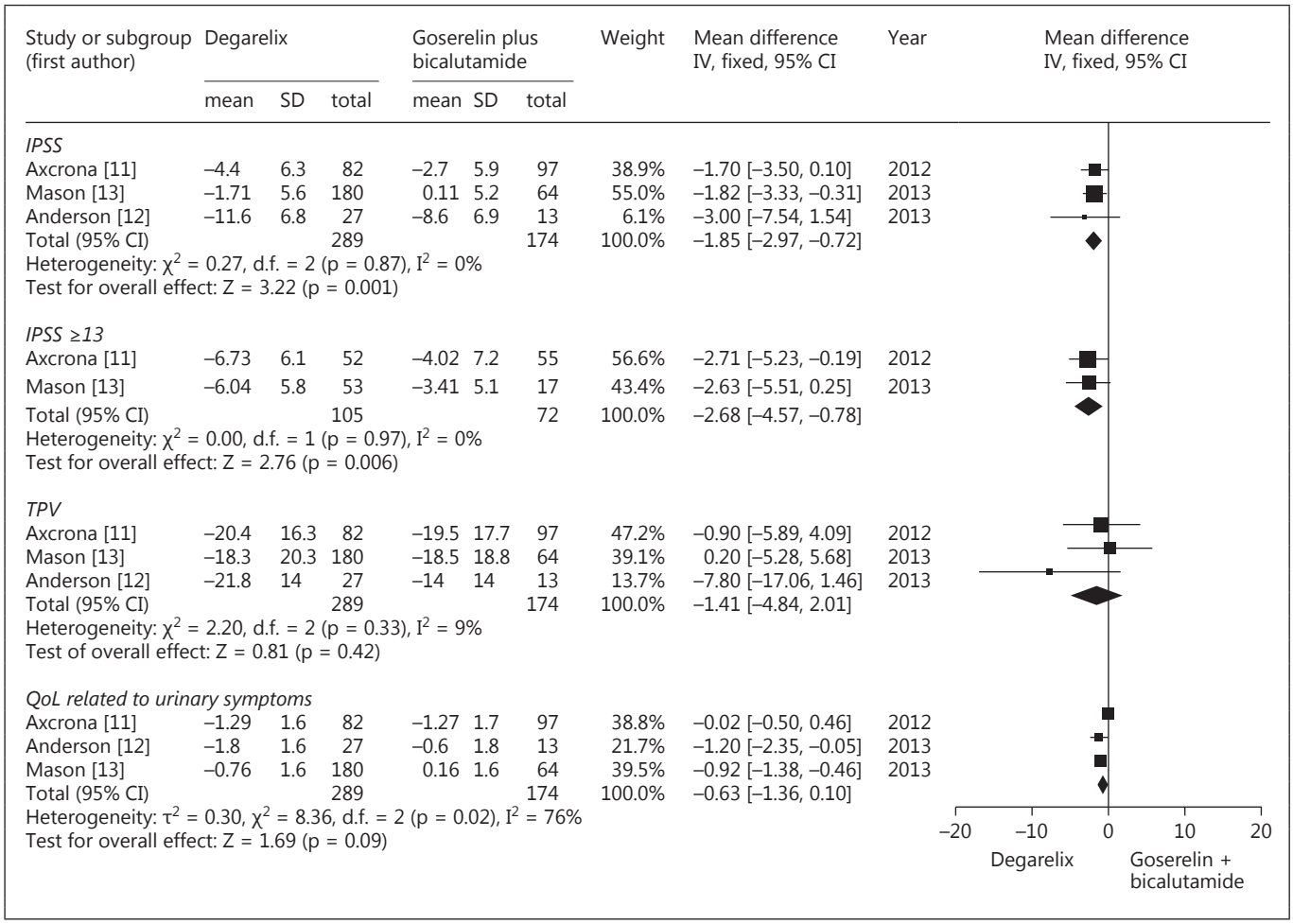

Fig. 2. Forest plots showing changes in IPSS, IPSS ≥13, TPV and QoL related to urinary symptoms in the treatment studies. SD = Standard deviation; IV = inverse variance.

Statistical Analysis and Meta-Analysis

A meta-analysis of comparable data was performed using Review Manager 5.1.0 (The Cochrane Collaboration, Oxford, UK). Due to the large number of plots, we combined the four forest plots into two plots using Adobe Photoshop CS (fig. 2, 3). We estimated the relative risk for dichotomous outcomes and the standardized mean difference (SMD) for continuous outcomes pooled across studies using the DerSimonian and Laird random-effects model [9]. We quantified inconsistencies using the I^2 statistic, which describes the proportion of heterogeneity across studies that is not due to chance and thus describes the extent of true inconsistencies in the results across the trials [10]. An I^2 <25% and an I^2 >50% reflect small and significant inconsistencies, respectively. For the confidence interval (CI), we used a 95% CI. If the result of an analysis showed a p >0.05, we considered that the homogeneity of the studies was satisfactory and chose the fixed-effects model. Otherwise, we chose the random-effects model. The presence of publication bias was evaluated using a funnel plot (fig. 4).

Results

Characteristics of the Individual Studies

The database search revealed 52 articles that could have potentially been included in our meta-analysis. Based on the inclusion and exclusion criteria, 39 articles were excluded after reading the titles and abstracts of the articles. Nine articles were not RCTs. One article lacked useful data (the values of IPSS, TPV and QoL). In total, three articles [11–13] with three RCTs were included in the analysis to compare degarelix with goserelin plus bicalutamide over 12 weeks. The baseline characteristics of the studies and patients included in our meta-analysis are listed in tables 1 and 2.

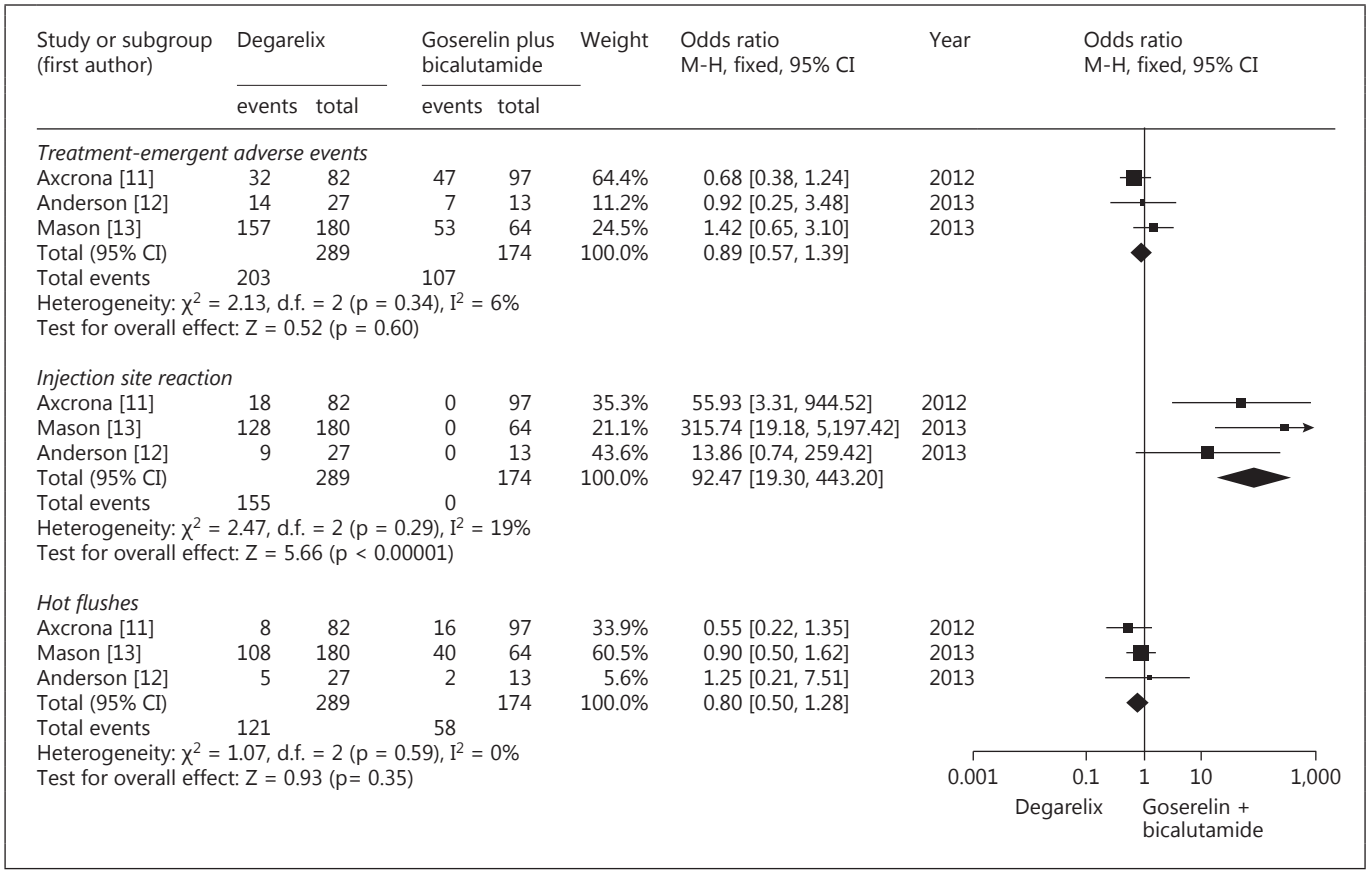

Fig. 3. Forest plots showing changes in treatment-emergent adverse events, injection site reaction and hot flushes in the treatment studies. M-H = Mantel-Haenszel.

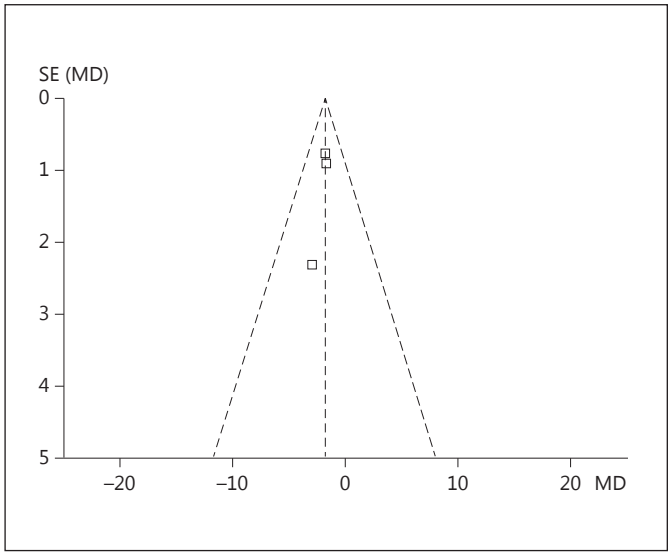

Fig. 4. Funnel plot of the studies represented in our meta-analysis. MD = Mean difference; SE = standard error.

Quality of the Individual Studies

Among the studies included in the analysis, all of them described the randomization processes that they had employed. All of the studies used double-blinded RCTs, all studies performed a power calculation to determine the optimal sample size, and two studies used intention-to-treat analysis. The quality level of each identified study was A (table 3). This plot was highly symmetrical, and all three of the squares were included in the large triangle. This process provided a qualitative estimation of the publication bias of the studies, and no evidence of bias was found (fig. 4).

Efficacy

IPSS. The three RCTs enrolled 463 participants (289 in the degarelix group and 174 in the goserelin plus bicalutamide group) (fig. 2). No heterogeneity was found among the trials (fig. 2). The pooled estimate of the SMD was –1.85, and the 95% CI was –2.97 to –0.72 (p = 0.001). This

Table 1. Study and patient characteristics

Study (first author)	Therapy in experimental group	Therapy in control group	Country	Sample size		Inclusion population	Exclusion population	Duration of therapy	Form of experiment and dosing	Form of control and dosing
				experimental	control					
Axcrona [11], 2012	degarelix	goserelin plus bicalutamide	Denmark	82	97	PCa (all stages), patients with PSA >2 ng/ml, TPV >30 ml, bone scan in the past 12 weeks	previous use of a urinary bladder catheter, treatment with a 5α-reductase inhibitor or botulinum toxin in the past 6 months, treatment with α-blocker in the past 4 weeks	12 weeks	I 240/80 mg	O 3.6 mg + 50 mg
Anderson [12], 2013	degarelix	goserelin plus bicalutamide	Switzerland	27	13	PCa (all stages), PSA >10 ng/ml, IPSS ≥12, Q_{max} ≤12 ml/s, prostate size >30 ml	treatment with a 5α-reductase inhibitor ≥6 months, treatment with α-blocker ≥8 weeks, prior transurethral resection of the prostate	12 weeks	I 240/80 mg	O 3.6 mg + 50 mg
Mason [13], 2013	degarelix	goserelin plus bicalutamide	UK	180	64	PCa TNM category T2b–T4, N0, M0, Gleason score ≥7, or PSA ≥10 ng/ml; TPV >30 ml	transurethral resection of the prostate; use of a urethral catheter; treatment with a 5α-reductase inhibitor or α-blocker in the past 12, 16 and 4 weeks, respectively	12 weeks	I 240/80 mg	O 3.6 mg + 50 mg

Q_{max} = Peak urinary flow; I = injection; O = oral.

result suggests that the decreases in IPSS were greater in degarelix- than in goserelin plus bicalutamide-treated patients. Two of the RCTs represented 177 participants (105 in the degarelix group and 72 in the goserelin plus bicalutamide group) (fig. 2). No heterogeneity was found among the trials (fig. 2). The pooled estimate of SMD was –2.68, and the 95% CI was –4.57 to –0.78 (p = 0.006). It was suggested that in patients with a baseline IPSS ≥13, the magnitude of the decrease was larger in the degarelix group.

TPV. The three RCTs represented 463 participants (289 in the degarelix group and 174 in the goserelin plus bicalutamide group) (fig. 2). According to our analysis, no heterogeneity was found among the trials (fig. 2), and a fixed-effects model was thus chosen for the analysis. Based on our analysis, the pooled estimate of the SMD was –1.41, and the 95% CI was –4.84 to 2.01 (p = 0.42). This result suggests that the efficacy of degarelix in terms of prostate shrinkage is similar to that of goserelin plus bicalutamide.

QoL Related to Urinary Symptoms. QoL related to urinary symptoms was assessed by the separate eighth IPSS question. The patients were asked to score their condition on a scale from 0 to 6 (delighted, pleased, mostly satisfied, mixed, mostly dissatisfied, unhappy and terrible). Any reported changes were assessed in three domains: delighted/pleased, mostly satisfied/mixed/mostly dissatisfied, and unhappy/terrible. The three RCTs represented 463 participants (289 in the degarelix group and 174 in the goserelin plus bicalutamide group) (fig. 2). The heterogeneity test provided a p = 0.02, so we adopted the random-effects model. The pooled estimate of SMD was –0.63, and the 95% CI was –1.36 to 0.10 (p = 0.09). This result suggests that the improvement in QoL related to urinary symptoms in the degarelix group was similar with that in the goserelin plus bicalutamide group.

Safety

Treatment-Emergent Adverse Events. The three RCTs represented 463 participants (289 in the degarelix group and 174 in the goserelin plus bicalutamide group) (fig. 3). The effect size for the meta-analysis was denoted as the odds ratio (OR). The pooled estimate of the OR was 0.89

Table 2. Baseline values of TPV, IPSS, QoL, PSA and testosterone

Study (first author)	TPV, ml		IPSS		QoL		PSA, ng/ml		Testosterone, ng/ml	
	D	G+B	D	G+B	D	G+B	D	G+B	D	G+B
Axcrona [11], 2012	54.8 (26)	49.9 (15.5)	14.3 (6.91)	13.4 (7.36)	2.85 (1.62)	2.73 (1.66)	277 (937)	148 (438)	4.25 (1.88)	4.43 (1.64)
Anderson [12], 2013	53.5 (14.0)	50.3 (14.0)	20.1 (6.8)	21.1 (6.9)	3.6 (1.6)	3.2 (1.8)	54.5 (8–1,914)	41.1 (14.6–348)	4.2 (1.1–6.7)	3.9 (2.7–7.4)
Mason [13], 2013	50.9 (20.3)	52.5 (18.8)	9.5 (6.71)	8.5 (6.30)	2.27 (1.63)	1.94 (1.56)	17.4 (30.1)	13.4 (12.9)	4.18 (1.72)	4.45 (1.49)

Values are presented as mean (standard deviation) or median with range (minimum–maximum).
D = Degarelix; G+B = goserelin plus bicalutamide.

Table 3. Quality assessment of individual studies

Study (first author)	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Intention-to-treat analysis	Level of quality
Axcrona [11], 2012	A	A	A	7	yes	analysis of covariance	yes	A
Anderson [12], 2013	A	A	A	0	yes	analysis of covariance	no	A
Mason [13], 2013	A	A	A	7	yes	analysis of covariance	yes	A

A = All quality criteria met (adequate) – low risk of bias; B = one or more of the quality criteria only partly met (unclear) – moderate risk of bias; C = one or more criteria not met (inadequate or not used) – high risk of bias.

and the 95% CI was 0.57 to 1.39 (p = 0.60). This result suggests that treatment-emergent adverse events with degarelix were similar to those with goserelin plus bicalutamide.

Injection Site Reactions. The three RCTs represented 463 participants (289 in the degarelix group and 174 in the goserelin plus bicalutamide group) (fig. 3). The pooled estimate of the OR was 92.47 and the 95% CI was 19.30 to 443.20 (p < 0.00001). The results suggest that the incidence of injection site reactions in the degarelix group was higher than in the goserelin plus bicalutamide group.

Hot Flushes. The three RCTs represented 463 participants (289 in the degarelix group and 174 in the goserelin plus bicalutamide group) (fig. 3). The pooled estimate of the OR was 0.80 and the 95% CI was 0.50 to 1.28 (p = 0.35). The results suggest that hot flushes with degarelix were similar to those in the goserelin plus bicalutamide group.

Discussion

ADT is the mainstay treatment of advanced PCa [14]. GnRH agonists may lead to an initial surge in testosterone as well as microsurges upon repeated injections [15, 16]. To avoid such complications, antiandrogens are commonly co-administered with GnRH agonists [7]. In contrast, GnRH blockers immediately block pituitary GnRH receptors, thereby causing rapid and pronounced testosterone suppression without initial surge or subsequent microsurges [17, 18]. In almost 70% of patients with PCa, the disease arises from the peripheral zone of the prostate gland and causes local symptoms (LUTS) only when it has grown to compress or invade proximal structures, such as the prostatic urethra, the urinary bladder or the neurovascular bundles [19, 20]. Another more common reason for the appearance of LUTS in patients with PCa is the parallel growth of the prostate due to be-

nign prostatic hyperplasia, which shows increasing prevalence with age [21].

The changes in the median levels of serum testosterone and the median percentage of PSA were comparable. Two of the included RCTs reported that the median testosterone level at week 12 was 0.05 ng/ml in both groups. Another RCT reported that the mean testosterone levels at week 12 were reduced by >97% in both groups. All of the included RCTs reported PSA levels that were reduced by 89.2–92% in the degarelix group and by 93–97.3% in the goserelin plus bicalutamide group. The efficacy of degarelix as a PCa treatment was in accordance with the results of an extensive clinical trial program [18, 19]. Our study revealed that both degarelix (240/80 mg) and goserelin (3.6 mg) plus bicalutamide treatments significantly reduced TPV (36–42% and 25–39%); prostate shrinkage was similar between the two groups. Decreases in IPSS were greater in the degarelix group. Moreover, in patients with a baseline IPSS ≥13, the magnitude of the decrease was larger under degarelix therapy. Since these differences cannot be ascribed to differences in TPV reduction from the two treatment approaches, seeking alternative explanations seems warranted.

Indeed, GnRH receptors have been identified on the epithelial and smooth muscle cells of the prostate, on the peripheral lymphocytes infiltrating the prostate, and on the bladder mucosa in both animals and in humans [22–27]. GnRH receptor blockade on these cells has been associated with the downregulation of pro-inflammatory cytokines, various growth factors and even α1-adrenoreceptors [27, 28], with potential implications for smooth muscle relaxation in prostate strips and TPV reduction [29]. These findings do seem to support the notion that the reduction of TPV due to ADT is not the only mechanism that can drive symptom relief and that the peripheral effects summarized herein could possibly explain the more rapid and pronounced relief of LUTS caused by degarelix than by goserelin in patients with moderate/severe LUTS. Although there was no significant difference between the degarelix and the goserelin plus bicalutamide groups, which is in line with the trends of IPSS changes, the improvements in QoL due to urinary symptoms tended to favor degarelix-treated patients.

The treatment-emergent adverse events induced by degarelix and goserelin plus bicalutamide were similar. Most of the treatment-emergent adverse drug reactions were hot flushes, which were similar between the two groups. Other commonly reported reactions, such as injection site reactions, were reported by the degarelix group only, but none of these reactions were severe or constituted a reason to discontinue treatment. Further, the incidence of markedly abnormal laboratory or vital sign changes was low and similar between the treatment groups.

This meta-analysis included studies representing findings from randomized, double-blind, placebo-controlled trials. According to the quality assessment scale that we developed, the quality of the individual studies in the meta-analysis was conforming. The results of this analysis acquire great importance from a scientific standpoint but also in everyday clinical practice. However, only three articles from European countries met our inclusion criteria. Therefore, only a limited number of the 466 patients were available for this meta-analysis, including only 289 patients in the degarelix group. Furthermore, these three studies were all published in 2012 or 2013. Thus, a long-term follow-up does not yet exist. In addition, the data from unpublished studies was not included in the analysis. These factors may have resulted in the development of a bias. More high-quality trials with larger samples are proposed to learn more about the efficacy and safety of the therapy on LUTS in men with PCa.

In conclusion, our meta-analysis indicates that the efficacy of degarelix in terms of prostate shrinkage in not inferior to that of goserelin plus bicalutamide; however, degarelix has a significantly more pronounced effects on LUTS.

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Disclosure Statement

The authors have no conflicts of interest to declare in relation to this article.

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