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Research Article

Efficacy and Safety of Degarelix in Taiwanese Patients with Prostate Cancer Requiring Androgen Deprivation Therapy: An Open-label, Multicenter Phase III Study

Tony Wu¹, Kun-Hung Shen², Chao-Yuan Huang³, Yen-Hwa Chang⁴, Po-Hui Chiang⁵, Yen-Chuan Ou⁶, Hsi-Chin Wu⁷, Chih-Shou Chen⁸, See-Tong Pang⁹ and Ming-Kuen Lai^{10*}

¹Division of Urology, Kaohsiung Veterans General Hospital, Kaohsiung City, Taiwan

²Urology Department, Chi Mei Medical Center, Tainan City, Taiwan

³Department of Urology, National Taiwan University Hospital, Taipei City, Taiwan

⁴Division of Urology, Taipei Veterans General Hospital, Taipei City, Taiwan

⁵Department of Urology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City, Taiwan

⁶Department of Urology, Taichung Veterans General Hospital, Taichung City, Taiwan

⁷Tainan Municipal An-Nan Hospital-China Medical University, Tainan City, Taiwan

⁸Urology Out-patient Department, Chiayi Chang Gung Memorial Hospital, Chiayi County, Taiwan

⁹Division of Urology, Gung Memorial Hospital, Taipei, Taiwan

¹⁰Department of Urology, Camillians Saint Mary's Hospital Luodon, Taiwan

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Abstract

Background: Pivotal phase III data have shown the efficacy and safety of degarelix (240 mg starting dose/80 mg maintenance dose [240/80 mg]) in North American and European patients with prostate cancer (PCa). This open-label, multicenter, single-arm trial has evaluated the efficacy and safety of degarelix in Taiwanese patients with PCa.

Methods: Eligible patients received degarelix 240/80 mg monthly for 6 months. The primary objective was the efficacy of degarelix in achieving and maintaining serum testosterone below castrate levels (≤ 0.5 ng/mL). Secondary objectives included changes in serum testosterone and PSA, and safety.

Results: One hundred and ten patients were allocated to treatment. Over six months, degarelix maintained serum testosterone at castrate levels; from Days 28-168, the cumulative probability of sustained castrate level

***Correspondence:** Ming-Kuen Lai, Department of Urology, Camillians Saint Mary's Hospital Luodon, Taiwan, E-mail: mingkuen2002@gmail.com

testosterone was 97.2% (95% CI: 91.6-99.1%), meeting the primary objective. Degarelix rapidly suppressed serum testosterone levels, with castrate levels achieved

by Day 3 in 93.5% of patients. PSA decreased rapidly from baseline, with a median reduction of 92.4% by Day 28. Degarelix was well tolerated, with the most frequent adverse events (AEs) being mild to moderate injection site reactions (ISRs), occurring mostly with the initial dose of degarelix. There were no immediate-onset systemic hypersensitivity reactions observed.

Conclusions: In Taiwanese patients with PCa, a monthly degarelix 240/80 mg/mL dose regimen rapidly decreased testosterone and PSA levels, and maintained testosterone at castrate levels (≤ 0.5 ng/mL) over 6 months. The safety profile of degarelix was consistent with that expected for elderly men with PCa undergoing androgen deprivation therapy (ADT).

Keywords: Androgen deprivation therapy; Degarelix; Prostate cancer

Introduction

Androgen deprivation therapy (ADT) slows disease progression and alleviates the symptoms of advanced prostate cancer (PCa). As such, the National Comprehensive Cancer Network (NCCN) recommends the use of ADT as primary systemic therapy in advanced disease, or as neoadjuvant/concomitant/adjuvant therapy alongside radiotherapy in localized or locally advanced PCa [1]. The most widely used form of ADT is luteinizing-hormone-releasing hormone (LHRH) agonists (such as leuprolide, buserelin, and goserelin), which activate the LHRH receptor, eventually downregulating the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. LHRH agonists cause an initial surge in LH, closely followed by a testosterone surge. These testosterone surges are a potential clinical disadvantage of LHRH agonists, as patients with a high tumor burden may experience an exacerbation of their symptoms ('clinical flare') [2], such as worsening of bone pain, urinary obstruction and, in severe cases, spinal cord compression. Following the initial increase in LH, secretion of LH and FSH are inhibited, causing suppression of testosterone production in the testes.

In contrast to LHRH agonists, gonadotropin releasing hormone (GnRH) antagonists competitively bind to

LHRH receptors and cause a rapid blockade of LH and FSH excretion, thereby avoiding the initial testosterone surge and/or flare of clinical symptoms. However, one major limitation with earlier-generation GnRH antagonists was their lack of sustained efficacy and their histamine-releasing properties, which resulted in anaphylactic-like syndrome [3]. While the second-generation GnRH antagonist abarelix showed better efficacy than earlier antagonists, immediate-onset allergic reactions were observed in 1.1% of patients, with the risk of these adverse events (AEs) increasing with treatment duration [4,5]. The next-generation GnRH antagonist degarelix, is also effective in treating PCa but is unlikely to cause histamine release [6]. Degarelix has an immediate onset of action, and has been shown to achieve a sustained testosterone suppression to below castrate levels (i.e., serum testosterone level ≤ 0.5 ng/mL) within the first few days after subcutaneous (s.c.) injection [7-9].

Data from the pivotal phase III study (CS21) performed in North America and Europe led to the approval of degarelix (240 mg starting dose/80 mg maintenance dose [240/80 mg]) in the US and Europe in December 2008 and January 2009, respectively. However, as a patient's ethnicity can affect response to drug treatment [10,11], the aim of the current study was to evaluate the efficacy and safety of degarelix in Taiwanese patients with PCa requiring ADT.

Materials and Methods

Study design

This was an open-label, multicenter, single-arm trial involving Taiwanese patients with PCa. Eligible patients received subcutaneous injections of degarelix 1-month depot at a starting dose of 240 mg (40 mg/mL), followed by five maintenance doses of 80 mg (20 mg/mL; 240/80 mg dose regimen) administered every 28-days. The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. Institutional Review Boards at all participating institutions approved the protocol, and all patients provided written informed consent.

Patients

Inclusion criteria: Taiwanese men aged ≥ 20 years with histologically-confirmed adenocarcinoma of the prostate (all stages) in whom androgen ablation was indicated (except for neoadjuvant hormonal therapy) were recruited. The population included patients with increasing prostate-specific antigen (PSA) after having undergone radical prostatectomy or radiotherapy with curative intent, i.e., those with biochemical failure or metastatic disease (hormone-sensitive). Patients were required to have a screening serum testosterone level >1.5 ng/mL and PSA ≥ 2 ng/mL, and an Eastern Cooperative Oncology Group score ≤ 2 .

Exclusion criteria: Patients considered to be candidates for curative therapy were excluded, and previous or current hormonal management of PCa was not permitted. Patients who had undergone localized therapy of curative intent, or neoadjuvant/adjuvant hormonal therapy for ≤ 6 months were accepted, as long as treatment had been discontinued >6 months before inclusion. Patients with known hypersensitivity to any component of degarelix, or those who had a history of severe/anaphylactic allergic reactions or severe urticarial/angioedema, were also excluded.

Objectives

The primary objective was to demonstrate that the degarelix 240/80 mg dosing regimen was effective and safe at achieving and maintaining serum testosterone below castrate levels (≤ 0.5 ng/mL) during 6 months of treatment. Secondary objectives were to evaluate changes in serum testosterone and PSA (during the first 28 days of treatment as well as the entire treatment period), along with the safety and tolerability profile of degarelix during the entire treatment period.

Endpoints

The primary endpoint was the cumulative probability of patients with testosterone levels below castrate levels (≤ 0.5 ng/mL) from Day 28-168, evaluated in the full analysis set (FAS). Secondary endpoints for the FAS and per protocol (PP) populations included: the proportion of patients with testosterone below castrate levels at Day 3, and the cumulative probability

of patients with testosterone below castrate levels from Day 56-168; serum levels of testosterone and PSA over time, and the percentage change in PSA from baseline to Day 28; the cumulative probability of no PSA failure (with PSA failure defined as being two consecutive increases of $\geq 50\%$, and at least 5 ng/mL, compared to nadir [12]). The frequency and severity of AEs, including clinically significant changes in laboratory values, electrocardiograms, vital signs, physical examinations, and body weight, were also assessed over the trial period.

Statistical methods

Sample size: In the pivotal phase III study CS21, the 95% confidence interval (CI) of the testosterone suppression response rate for the 240/80 mg non-Asian reference population was 93.5-98.8% [7]. Assuming a response rate in Taiwanese patients of 98% (lower than the observed point-estimate of 99%, but still well within the 95% CI) and a 15% annual drop-out rate, 110 patients were required to have sufficient power ($\geq 90\%$) to meet the primary endpoint in the FAS. In the PP analysis, 102 patients were required to have sufficient power ($>85\%$) to meet the primary endpoint.

Statistical analysis: The primary efficacy analysis population was the FAS, with the corresponding PP analysis serving as the sensitivity analysis. Hypotheses associated to secondary endpoints were not ranked further. The FAS population comprised all patients who received at least one dose of degarelix and had at least one efficacy variable assessed. The PP population comprised those patients in the FAS who did not violate pre-defined criteria for major protocol deviations (in line with the CS21 study). The intent to treat and safety populations comprised all patients who received at least one dose of degarelix.

The primary efficacy analysis measured the 6-month cumulative probability of below castrate testosterone levels (≤ 0.5 ng/mL) using the Kaplan Meier (KM) method (based upon testosterone measurements at the scheduled study visits). The associated two-sided 95% CI was based on log-log transformation, Greenwood's formula, and asymptotic maximum likelihood theory. If the lower limit of this two-sided 95% CI was $\geq 90\%$, and

thus fulfilling the same FDA criterion as in CS21, the primary objective was met.

Secondary efficacy analyses included: the proportion of patients with testosterone level ≤ 0.5 ng/mL on Day 3; the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 56-168, using KM estimates and 95% CIs, along with response rates and associated 95% CIs per visit; median (inter-quartile range [IQR]) values and percentage changes from baseline over time in serum levels of testosterone and PSA; median (IQR) percentage change from baseline to Day 28 in PSA; the cumulative probability of no PSA failure, with time to PSA failure (days from first dosing where an increase in serum PSA of $\geq 50\%$ from nadir and ≥ 5 ng/mL measured on two consecutive occasions at least 2 weeks apart) estimated using the KM method, along with response rates (and associated 95% CIs). AEs were coded using the Medical Dictionary for Regulatory Activities, and classified according to severity using Common Terminology Criteria for Adverse Events v4.02, and whether they were degarelix-related or not.

Results

Patient demography

Between December 2010 and October 2012, 125 patients were screened, of whom 110 were allocated to treatment (Table 1). Treatment was discontinued in six (5%) patients due to: withdrawal of informed consent (four patients); AEs (one patient); and major protocol violation (one patient). The majority ($n=65$; 59%) of patients had metastatic PCa (Table 1), and the median duration of PCa since diagnosis for the FAS was 37.5 days (range: 6 days to 15.2 years). Twenty-one patients (19%) had cardiovascular disease history. Overall, the patient population was characteristic of a male Asian population with PCa (Table 1).

Efficacy of degarelix in Taiwanese patients

Six-month cumulative probability of maintaining testosterone at castrate levels (≤ 0.5 ng/mL): The degarelix 240/80 mg dose regimen was effective in achieving and

maintaining testosterone at castrate levels (≤ 0.5 ng/mL). In the FAS (Figure 1), a high proportion of patients achieved testosterone suppression ≤ 0.5 ng/mL from Days 28-168 (97.2%; 95% CI 91.6-99.1%), with the lower CI above the 90% threshold level required to meet the primary objective. Similar data were seen in the PP population. All follow-up patients except one maintained testosterone suppression at castration level after Day 28; one patient had a temporary increase in testosterone levels to >0.5 ng/mL on Day 56.

Testosterone suppression over time:

Testosterone was rapidly suppressed by the degarelix 240/80 mg dose regimen in the FAS. By Day 3, 93.5% of patients had achieved testosterone suppression to ≤ 0.5 ng/mL. All patients had achieved castration level testosterone by Day 28. The median testosterone level was 0.26 ng/mL on Day 3, 0.21 ng/mL on Day 7, and 0.05 ng/mL from Days 28-168 (Figure 2).

PSA suppression over time: A rapid decrease in PSA over time was observed in the FAS, with median PSA levels being 69.7 ng/mL on Day 3, 40.7 ng/mL on Day 7, 7.18 ng/mL on Day 28, and 1.01 ng/mL on Day 168 (Figure 3). Median decrease in PSA from baseline was 21.8% at Day 3 and 92.4% at Day 28. By Day 168, PSA had decreased by 98.4% (Figure 4).

A total of four patients met the study's PSA failure criteria (two consecutive increases of $\geq 50\%$ compared to nadir and at least 5 ng/mL); one on Day 112, one on Day 140, and two on Day 168. The cumulative probability of no PSA failure in the FAS was 96.2% (95% CI: 90.1-98.5%) at Day 168 (Figure 5).

Safety

The mean duration of exposure was 5.85 months. During the study, a total of 561 AEs were reported by 98 (89%) patients; most were mild or moderate in intensity, with 21 severe AEs reported in seven (6%) patients. The most frequently reported AEs were general disorders or administration site conditions, reported by 61 (55%) patients, with the majority reporting mild or moderate injection site reactions (ISRs; 45% [$n=50$]). Most patients (43% [$n=47$]) reported ISRs following the initial dose of degarelix; after this time point, the number of patients reporting ISRs was consistently lower (range

Figure 1: Kaplan-Meier plot (95% confidence interval) of the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 28-168 (full analysis set).

Figure 2: Median (interquartile range) levels over time of serum testosterone (ng/mL), in the full analysis set.

Figure 3: Median (interquartile range) levels over time of serum prostate-specific antigen (PSA) (ng/mL), in the full analysis set.

Figure 4: Median (interquartile range) levels over time of the percentage change from baseline in serum PSA (ng/mL), in the full analysis set.

Figure 5: Kaplan-Meier plot (95% confidence interval) of the cumulative probability of no prostate-specific antigen (PSA) failure (full analysis set).

Time to PSA failure was defined as being the number of days from first dosing where an increase in serum PSA of $\geq 50\%$ from nadir and ≥ 5 ng/mL were measured on two consecutive occasions at least 2 weeks apart [12].

12-16% [$n=13-17$]).

Very few AEs relating to sexual dysfunction (four [4%]) and hyperhidrosis (seven [6%]) were reported. Increased aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase and bilirubin were observed in 32%, 26%, 12% and $<1\%$ of patients, respectively. Almost one-quarter (22%) of patients had weight increases (a known side effect of ADT) of $\geq 7\%$ from baseline. Potential hypersensitivity reactions were observed within 0-24 or >72 hours (eight [1%] AEs for both time points) after degarelix administration, and all were mild/moderate in severity. At 0-24 hours, the most frequent events reported were peripheral edema ($n=3$), dyspnea ($n=2$) and pruritus ($n=2$); at >72 hours, the most frequent events reported were dyspnea ($n=2$) and pruritus ($n=2$). The incidence of other markedly abnormal changes in vital signs was consistent with a group of elderly patients, many of whom had a medical history of cardiac disease or hypertension.

Nineteen serious AEs (SAEs) were reported by nine

(8%) patients. Treatment was discontinued in one patient with existing hypertension, hyperlipidemia and diabetes with nephrotic syndrome, who developed acute renal failure and focal segmental glomerulosclerosis with ischemic acute tubular necrosis around two months after first dose of degarelix. The events was considered unlikely related to degarelix and the patient was treated with hemodialysis and oral prednisolone, and renal function returned to normal 2 months later. One patient died following an acute myocardial infarction (considered unlikely related degarelix) 9 days after the end of the study.

Discussion

The data we reported show that degarelix is effective and well tolerated in Taiwanese patients with PCa. Over 6 months, a degarelix 240/80 mg/mL dose regimen effectively maintained serum testosterone at castrate levels (≤ 0.5 ng/mL). From Days 28-168, the cumulative probability of sustained castrate level testosterone was 97.2% (95% CI: 91.6-99.1%) for both the FAS and PP

Table 1: Baseline characteristics in the full analysis set.

	Taiwanese patients receiving degarelix 240/80 mg N=110
Demography	
Age, years Median (min, max)	74.5 (49, 90)
Weight, Kg Median (min, max)	64.4 (45, 93.2)
BMI, Kg/m² Median (min, max)	24.4 (17.1, 35.1)
Stage of PCa	
Stage of PCa, n (%) Localized Locally advanced Metastatic Not classifiable	14 (13%) 26 (24%) 65 (59%) 5 (5%)
Gleason score, n (%) 2–4 5–6 7–10	1 (<1%) 10 (9%) 99 (90%)
ECOG status, n (%) Fully active Restricted but ambulatory Ambulatory unable to carry out work	94 (85%) 13 (12%) 3 (3%)
Time since PCa diagnosis, days Median (min, max) Cardiovascular disease history, n (%)	37.5 (6, 5540) 21(19%)
<i>Hormone parameters at baseline</i>	
PSA, ng/mL Median (min, max)	87.7 (2.63, 5817)
Testosterone, mg/ml Median (min, max)	4.01 (1.59, 9.83)

BMI=body mass index; ECOG=Eastern Co-operative Oncology Group; kg=kilogram; N=number; PCa=prostate cancer; PSA=prostate-specific antigen.

analysis sets, meeting the primary objective of the study. There were rapid decreases in serum testosterone, with castrate levels achieved by Day 3 in 93.5% of patients. Almost all patients maintained castration level from Days 28-168, except one patient who had modest testosterone escape (>0.50 ng/mL) on Day 56. PSA

also decreased rapidly from baseline, with a median reduction of 92.4% by Day 28. Rising PSA, indicative of biochemical failure, was experienced by four patients between Days 112-168. Overall, degarelix was well tolerated. The most frequent AEs were mild to moderate ISRs, occurring mostly with the initial dose of degarelix. AEs associated with testosterone suppression such as hyperhidrosis occurred in few patients and were manageable. There were no immediate-onset systemic hypersensitivity reactions observed. Additional reported AEs were consistent with those expected for elderly men with PCa undergoing ADT. A limitation to our findings is that the study was open-label, which might impact the interpretation of reported AEs. Also, one s.c. injection of degarelix was administered at each time point and so blinding was not possible.

Sustained castrate levels of testosterone in Taiwanese patients treated with degarelix are comparable to those observed in other degarelix studies in different populations [7,13,14]. The cumulative probability of sustained castrate level testosterone in Western patients was 97.2% (95% CI: 93.5-98.8%) between Days 28-364, in Japanese patients it was 94.9% (95% CI: 90.9-98.9%) between Days 28-364, and in Korean patients it was 96.7% (95% CI: 92.2-98.6%) between Days 28-196 [7,13,14]. Serum testosterone also rapidly decreased in these different populations. By Day 3, serum testosterone had decreased by 96.1% in Western patients, by 99.3% in Japanese patients, and by 97.4% in Korean patients [7,13,14]. Phase II degarelix studies have also shown sustained castrate level testosterone over 1 year, along with rapid testosterone suppression [15,16]. PSA reduction in Taiwanese patients also appears to be consistent with the decline in PSA levels by Day 28 observed in Western (85%), Japanese (80.1%) and Korean (79.7%) patients [7,13,14]. These data are supported by a pooled analysis of degarelix clinical trials, suggesting efficacy advantages for GnRH antagonists over LHRH agonists [17,18].

The safety and tolerability of degarelix is consistent with that reported for other degarelix trials, with the most frequent AEs being mild to moderate ISRs [7,13-16]. Recent data from a pooled analysis of degarelix clinical trials found that GnRH antagonists had a better safety and tolerability profile over LHRH agonists, especially

in terms of cardiovascular risk in patients with existing cardiovascular disease [17,18]. The ARF observed in our study was considered unlikely related to degarelix. Few AEs of ARF have been reported in previous degarelix studies [19]. In the pivotal CS21 study, ARF was reported in one patient receiving 240/160 mg degarelix and in one patient receiving leuprolide. Both events were considered unrelated to study treatment. In the CS37 study, which evaluated intermittent vs continuous ADT, ARF was reported in one patients (Continuous leuprolide: n=1, ARF was also the cause of this patient's death). The event was not drug related. Currently, an association between ADT and acute kidney injury (AKI) is beginning to be reported [20-22]. To our knowledge, there are no comparable studies comparing the risk of AKI using GnRH antagonists, and further studies may be needed to evaluate this. Interestingly, distinct immunological and physiological differences between GnRH agonists and antagonists have been reported [23-27]. For example, in contrast to GnRH antagonists, GnRH agonists drive lymphocyte activation and cytokine production *in vitro* [24-27], and appear to be associated with atherothrombotic plaque progression and instability [23]. As the leading cause of ischaemic renal injury is atherosclerotic renal artery stenosis and plaque rupture [28], this could perhaps explain the recent observations of an association between GnRH agonists and AKI, although further research is required. Since it has also been reported that patients with baseline CV comorbidities have an increased risk of AKI compared with those without CV diseases at baseline (HR=1.23; 95% CI, 1.13-1.33; $P < .001$) [29], a single mechanism that could explain both AKI and CV events would be attractive.

In Taiwan, the management and treatment of PCa follows guidance published by the NCCN [1], which suggests accomplishing ADT either by surgical castration or by medical castration using either LHRH agonists or GnRH antagonists. All methods of ADT are considered by the NCCN to be equally effective; however, medical castration is often a preferred option, with the benefit of GnRH antagonists being that they do not induce testosterone flare. As a result, when treating patients with GnRH antagonists there is no need to co-administer anti-androgen therapy [1]. The only licensed GnRH antagonist in Taiwan is degarelix. Thus, based

upon clinical data, degarelix treatment should be considered to achieve ADT rapidly and safely, avoiding testosterone flare and allergic-type reactions [30,31].

In conclusion, this study has shown that degarelix 240/80 mg/mL dose regimen was both effective and well tolerated in Taiwanese men with PCa undergoing ADT.

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