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REVIEW

Progress in Clinical Research on Gonadotropin-Releasing Hormone Receptor Antagonists for the Treatment of Prostate Cancer

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Abstract: Gonadotropin-releasing hormone (GnRH) receptor agonists are still the most commonly used androgen deprivation treatment (ADT) drugs for prostate cancer in clinical practice. Currently, the GnRH receptor antagonists used for endocrine therapy for prostate cancer primarily include degarelix and relugolix (TAK-385). The former is administered by subcutaneous injection, while the latter is an oral drug. Compared to GnRH agonists, GnRH antagonists reduce serum testosterone levels more rapidly without an initial testosterone surge or subsequent microsurges. This review focuses on the mechanism of action of GnRH antagonists and agonists, the developmental history of GnRH antagonists, and emerging data from clinical studies of the two antagonists used as endocrine therapy for prostate cancer.

Keywords: gonadotropin-releasing hormone, prostate cancer, degarelix, relugolix

Introduction

Prostate cancer is one of the most common malignant tumours in men, and its incidence ranks second among all malignant tumours in men worldwide.[1] The latest research shows that the incidence and mortality of prostate cancer in most countries in the world have reached a relatively stable state after years of growth.[2] However, due to the insidious onset of prostate cancer, many patients are already in the advanced stage when they are diagnosed. Since Huggins and Hodges discovered that the growth of prostate cancer cells requires testosterone in 1941,[3] by the end of the 1970s, surgical castration was commonly used as androgen deprivation therapy (ADT) to achieve castration levels of testosterone in the treatment of advanced prostate cancer.[4] In 1971, Schally et al completed the isolation and structural identification of luteinizing hormone releasing hormone (LHRH),[5] demonstrating for the first time that both natural and synthetic forms of LHRH can successfully stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) in mammals, including humans.[6] This major discovery has opened a new era of endocrine therapy for prostate cancer, and surgical castration has gradually been replaced by medical castration due to the irreversibility and the psychological impact of surgical castration on patients. At present, more than 6000 LHRH agonists and hundreds of LHRH antagonists have been synthesized worldwide, and these drugs have become the basic for advanced prostate cancer treatment. The objective of this study was to review GnRH antagonists' and agonists' mechanisms of action, the developmental history of GnRH antagonists, and emerging data from clinical studies of the two antagonists in endocrine therapy for prostate cancer.

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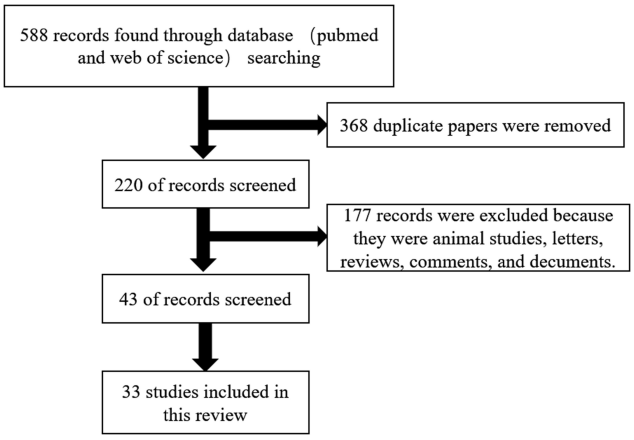

Figure 1 Flow diagram of evidence collection.

Materials and Methods

PubMed and Web of Science were used to search for "degarelix" and "relugolix", and keywords included "degarelix", "relugolix", "GnRH antagonist", "degarelix AND prostate cancer", "relugolix AND prostate cancer" and "GnRH antagonists AND prostate cancer". We also reviewed any useful references cited in the retrieved papers, and papers on animal research, letters, comments, reviews, and duplicate papers were excluded. The selection process is described in the flow chart (Figure 1), and a total of 33 clinical studies were included in this review, including 9 Phase III clinical trials.

Mechanism of Action

Gonadotropin-releasing hormone (GnRH) agonists, which were first applied in the 1980s, are currently the most widely used ADT drugs; they primarily activate GnRH receptors of the hypothalamic-pituitary-gonadal axis and produce excessive and constant stimulation, overcoming pulsatile GnRH control, which leads to downregulation and desensitization of GnRH receptors, and finally, negative feedback that reduces serum testosterone levels.[7] However, in the first 1–2 weeks of initial administration, these treatments cause a sharp increase in serum testosterone levels, which can stimulate the rapid growth of tumour cells and cause a series of clinical symptoms, such as bone pain, worsening symptoms of lower urinary tract obstruction, spinal cord compression and even some fatal adverse events.[8] In the early stage of the maintenance dose injection, there may be fluctuations in serum testosterone levels. Therefore, it is necessary to routinely combine these treatments with non-steroidal anti-androgen drugs, such as bicalutamide and flutamide, in clinical practice;[9] however, it is impossible to completely avoid the above effects. Unlike GnRH agonists, GnRH antagonists competitively bind to GnRH receptors in the anterior pituitary and quickly inhibit the excitatory effects of endogenous GnRH on the pituitary, directly blocking the secretion of FSH and LH within a few hours and reducing serum testosterone levels.[7]

The History of GnRH Antagonists

Since 1972, hundreds of GnRH antagonists have been synthesized, and a series of related animal experiments have been performed. Early GnRH antagonists are hydrophilic and induce the release of histamine, leading to transient oedema and other severe allergic-like reactions.[10] To eliminate this unfavourable oedema-promoting effect, Schally et al synthesized new analogues using D-ureidoalkyl amino acids.[11] Among these antagonists without obvious oedema-promoting effects, cetrorelix was found to have the highest overall inhibitory activity and receptor binding affinity.[10] In 1994, cetrorelix became the first GnRH antagonist to be tested in prostate cancer patients.[12,13] Although its clinical efficacy has been confirmed, it has associated adverse events, such as oedema-promoting effects and allergic reactions. Furthermore, it is difficult to manufacture long-acting preparations, so it ultimately failed to enter the market. Next, abarelix was approved by the US Food and Drug Administration (FDA) to enter the market in 2003 and was the first GnRH antagonist used to treat advanced prostate cancer; however, due to the same adverse reactions,[14] it was ultimately not widely used. In 2008, degarelix was approved by the FDA as a next-generation GnRH antagonist; compared to previous generations, histamine release characteristics were greatly reduced, so it is widely used in the US and European markets. In 2019, degarelix was launched in China, becoming China's first first-line GnRH antagonist for endocrine therapy of prostate cancer. In 2020, the new oral GnRH antagonist relugolix (TAK-385) completed a phase III clinical trial for the treatment of advanced prostate cancer, demonstrating good safety and efficacy.[15] It may be expected to become another option for prostate cancer ADT.

Degarelix

Dose Identification Study

Regarding selection of the optimal dose of degarelix for the one-month depot formulation, three open-label,

randomised, parallel-group, Phase II clinical trials were conducted. In Europe and South Africa, the initial dose of 240 mg obtained better testosterone suppression than the 200 mg group within one month. During the one-year observation, it was found that in the maintenance dose, the castration rates of the 160 mg, 120 mg, and 80 mg groups were 100%, 96%, and 92%, respectively.[16] In North America, a clinical study involving 128 patients demonstrated that the maintenance dose of the 80 mg group was better than the 60 mg group in terms of testosterone suppression.[17] In addition, a Japanese study reported that the efficacy of the 240/80 mg degarelix dosing regimen for prostate cancer patients was basically the same as the 240/160 mg group.[18] Taking into account the safety, efficacy and economic benefits of the drug, the 240/80 mg dosing regimen eventually became the recommended dosage regimen of the one-month depot formulation. For the 3-month depot formulation of degarelix, after initial subcutaneous injection of 240 mg, it was found that the maintenance dose of 480 mg every 84 days had a higher cumulative castration rate than the 360 mg group,[19] and its safety and efficacy have also been confirmed in subsequent phase III clinical trials.[20,21] Detailed data are presented in Tables 1 and 2.

Oncology Efficacy

Pivotal Phase III Trial (CS21)

In a 1-year, multicentre, randomised, open-label phase III trial (CS21), 610 histology-confirmed prostate cancer patients were randomly assigned to the following three

Table 1 Efficacy of GnRH Receptor Antagonists in a Phase III Clinical Study

Study	Years	Follow-Up (Month)	Arm	N	Cumulative Castration (%)	PSA Failure (%)	Overall Mortality (%)	Mean Decreased IPSS	Prostate Volume Reduction (%)
CS21 Klotz et al[8]	2008	12	Degarelix 80/160 mg	409	97.2/98.3	8.9/14.2	2.0	N/A	N/A
			Agonist	201	96.4	14.1	4.0	N/A	N/A
CS28 Anderson et al[39]	2013	3	Degarelix	27	N/A	N/A	N/A	N/A	42.0
			Agonist	13	N/A	N/A	N/A	N/A	25.0
CS30 Mason et al[40]	2013	3	Degarelix	181	N/A	N/A	N/A	6.0	36.0
			Agonist	64	N/A	N/A	N/A	3.4	35.3
CS31 Axcrona et al[38]	2012	3	Degarelix	81	N/A	N/A	N/A	6.7	37.2
			Agonist	92	N/A	N/A	N/A	4.0	39.0
CS35 Tombal et al[21]	2012	12	Degarelix	565	N/A	13.5	N/A	N/A	N/A
			Agonist	283	N/A	13.5	N/A	N/A	N/A
CS42 You et al[35]	2015	7	CS42 Degarelix	155	96.7	2.7	N/A	N/A	N/A
			CS21 Degarelix	207	99.0	2.1	N/A	N/A -	N/A
Ozono et al[20]	2018	12	Degarelix	117	95.1	2.6	0	N/A	N/A
			Agonist	117	100.0	0.9	0.9	N/A	N/A
Sun et al[34]	2019	12	Degarelix	143	97.0	17.2	N/A	5.9	N/A
			Agonist	142	93.4	26.6	N/A	5.2	N/A
Shore et al[15]	2020	12	Relugolix	622	96.7	N/A	N/A	N/A	N/A
			Agonist	308	98.0	N/A	N/A	N/A	N/A

Abbreviations: PSA, prostate specific antigen; IPSS, International Prostate Symptom Score.

Table 2 Adverse Effects of GnRH Receptor Antagonist in a Phase III Clinical Study

Study	Years	Follow-Up (Month)	Arm	N	AEs (%)	Hot Flash (%)	Injection Site Reaction (%)	Musculoskeletal Events (%)	CV Events (%)
CS21 Klotz et al[8]	2008	12	Degarelix 80/160 mg	409	81.0	26.0	40.0	11.0	9.0
			Agonist	201	78.0	21.0	0.5	19.0	13.0
CS28 Anderson et al[39]	2013	3	Degarelix	27	52.0	19.0	33.0	0	N/A
			Agonist	13	54.0	15.0	0	15.0	N/A
CS30 Mason et al[40]	2013	3	Degarelix	181	78.0	60.0	33.0	N/A	N/A
			Agonist	64	73.0	63.0	2.0	N/A	N/A
CS31 Axcrona et al[38]	2012	3	Degarelix	81	39.0	10.0	15.0	4.6	0
			Agonist	92	48.0	17.0	0	7.4	1.1
CS35 Tombal et al[21]	2012	12	Degarelix	565	75.0	N/A	39.0	14.0	N/A
			Agonist	283	71.0	N/A	2.0	20.0	N/A
CS42 You et al[35]	2015	7	CS42 Degarelix	156	72.0	3.0	22.0	N/A	N/A
			CS21 Degarelix	207	70.0	22.0	27.0	N/A	N/A
Ozono et al[20]	2018	12	Degarelix	117	100.0	23.1	75.0	5.1	N/A
			Agonist	117	91.0	32.5	6.0	4.3	N/A
Sun et al[34]	2019	12	Degarelix	143	76.1	N/A	35.0	7.7	7.7
			Agonist	142	58.9	N/A	0.7	10.6	10.6
Shore et al[15]	2020	12	Relugolix	622	92.9	54.3	N/A	N/A	2.9
			Agonist	308	93.5	51.6	N/A	N/A	6.3

Abbreviations: AEs, adverse events; CV, cardiovascular.

groups: 240 mg subcutaneous degarelix for 1 month with a monthly maintenance dose of 80 mg or 160 mg, or 7.5 mg/month leuprolide was injected intramuscularly. Patients receiving leuprolide were given anti-androgen drugs as appropriate to prevent flares.[8] The performance of the two different degarelix dosing regimens (240/80 mg and 240/160 mg) in the primary endpoint (testosterone suppression) was not inferior to the leuprolide group (Table 1). Three days after the initial injection dose, the castration rates of the 240/160 mg group and 240/80 mg group were 96.1% and 95.5%, respectively, while that of the leuprolide group was 0%; on the 14th day, they were 100%, 99.5%, and 18.2%. In addition, 80% of patients in the leuprolide group had a testosterone surge, compared to 0% in the degarelix group. Consistent with the changes in testosterone, the prostate-specific antigen (PSA) decline in the 240/80 mg and 240/160 mg degarelix groups was also significantly faster than in the leuprolide group and was basically the same as the leuprolide + bicalutamide group. This phenomenon may be attributed to degarelix's ability to also reduce serum adrenal androgen levels in patients with prostate cancer.[22] Furthermore, in the first 1–2 weeks of treatment, the median LH and FSH levels of patients in the leuprolide group increased due to the mechanism of action; however, median LH and FSH levels in the degarelix group declined more rapidly after the start of the treatment and remained suppressed until the end of the study.[8] At the end of the 12-month study, median FSH levels in the 240/80 mg degarelix, 240/160 mg degarelix and leuprolide groups decreased by 88.5%, 89.0% and 54.8%, respectively.[8]

Additional Analyses of CS21

In the CS21 study, the incidence of PSA failure (defined as a PSA increase of ≥ 50% from nadir and ≥5 ng/mL on two consecutive occasions at least 2 weeks apart) during the study was 8.9%, 14.2%, and 14.1% in the 240/80 mg degarelix, 240/160 mg degarelix and leuprolide groups, respectively.[8] Because 240/80 mg degarelix is the recommended dosing regimen, Tombal et al conducted an additional analysis of the secondary end point of biochemical recurrence rate and found that patients in the CS21 study had a lower PSA failure rate with 240/80 mg degarelix compared to 7.5 mg/month leuprolide; the difference was most marked in those with baseline PSA >20 ng/mL or metastatic prostate cancer.[23] For changes in serum alkaline phosphatase levels, the decrease in serum alkaline phosphatase in the degarelix 240/80 mg group was greater than in the leuprolide group, especially in patients with bone metastases or patients with a baseline PSA level >50 ng/mL.[24] Over 1 year, patients using degarelix always maintained an alkaline phosphatase inhibition state, and there was no increase in serum alkaline phosphatase levels of patients in the late stage, unlike the leuprolide group.[24]

Extension Phase of CS21

In recent years, a number of studies have suggested that PSA progression may predict overall survival in prostate cancer patients.[25,26] In the extension phase of the CS21 study, in addition to its good tolerance and stable testosterone suppression within 5 years,[27] it was also found that the PSA progression-free survival (PSA-PFS) hazard rate of the degarelix group was relatively lower than the leuprolide group, and the PSA-PFS hazard rate was decreased significantly after patients in the leuprolide group were switched to the degarelix group, while the rate was consistent in patients who continued to use degarelix.[27,28] Furthermore, studies by Iversen et al showed that degarelix monotherapy also produces a superior effect on PSA-PFS outcome than the GnRH agonist + bicalutamide dosing regimen.[29] The above findings may indicate that degarelix has certain advantages in delaying the progression of PSA compared to GnRH agonists, although its specific mechanism of action is unclear.[23,28,29] On the other hand, degarelix reduces LH and FSH levels more directly and rapidly,[8] and it was confirmed that its inhibition of FSH levels was more profound than leuprolide because FSH levels were further suppressed in patients who switched from the leuprolide group to the degarelix group until levels were similar to those observed during continuous degarelix treatment.[28] An authoritative study found that FSH receptors are selectively expressed on the surface of blood vessels in a variety of organ tumours, including prostate cancer,[30] and FSH is considered to play an important role in the growth regulation of prostate cancer cells.[31,32] A single-centre retrospective study found that there was a trend for a negative correlation between FSH values and the time from hormone-sensitive prostate cancer to castration resistance.[33] However, there is still a lack of data from large-scale clinical studies on whether prostate cancer patients who use degarelix have better long-term benefits.

Asian Clinical Study

Recently, major studies of degarelix in Asian populations have also proven its short-term efficacy and safety (shown in Table 1). In a one-year phase III clinical study in China, 273 prostate cancer patients were randomised in a 1:1 ratio to once-a-month subcutaneous injection of either degarelix (240/80 mg) or goserelin (3.6 mg).[34] During the study, treatment with degarelix resulted in more rapid testosterone suppression and PSA reduction versus the goserelin group, and the cumulative castration rate of the degarelix group was 3.6% higher than the goserelin group, indicating that the primary efficacy of degarelix is at least not inferior to GnRH agonists. Moreover, on day 364, the cumulative probability of PSA-PFS in the degarelix group was higher than in the goserelin group, and the cumulative probability of PFS in the degarelix and goserelin groups was 81.5% and 71.7%, respectively.[34] Therefore, degarelix showed a more favourable trend in this study with respect to short-term disease control.

In Japan, a phase III clinical study was performed to evaluate the efficacy and safety of a 3-month dosing regimen of degarelix in prostate cancer patients, and 234 subjects with prostate cancer were randomised to the degarelix and goserelin groups.[20] The initial dose of 240 mg degarelix or 3.6 mg goserelin was subcutaneously injected; after the 28th day, a maintenance dose of 480 mg degarelix or 10.8 mg goserelin was given every 84 days. In general, compared to goserelin, the degarelix group showed a more rapid decline in serum testosterone, FSH, LH and PSA levels in the early stages of the study, and the primary endpoint (cumulative castration rate from day 28 to day 364) was not significantly different between the two groups.[20] Since the cumulative castration rate of the goserelin group was 100%, an additional analysis was performed on the 95% confidence interval to determine the difference in the proportion of castrated subjects, revealing

that the 3-month formulation of degarelix was not inferior to that of goserelin in 1-year testosterone suppression.[20] Furthermore, the proportion of subjects with PSA failure within 364 days was also not significantly different between the two groups.[20] Similarly, in a 7-month clinical study conducted in South Korea, degarelix's performance in inhibiting serum testosterone levels and reducing PSA was similar to that of CS21.[35]

Pooled Analysis

Klotz et al conducted a pooled analysis of 5 randomised phase III/IIIb clinical trials comparing degarelix to GnRH agonists in which a total of 1458 patients received either 3 months (n = 467) or 12 months (n = 1458) of treatment.[36] Results showed that PSA-PFS was improved in the degarelix group (HR: 0.71 p=0.017). For patients with a baseline PSA value >20 ng/mL, the hazard rate of PSA-PFS was 0.74 (p=0.052). Overall survival (OS) was also higher in the degarelix group (HR: 0.47; p=0.023). In patients with baseline testosterone levels> 2 ng/mL, OS was particularly improved after degarelix treatment (HR: 0.36 p=0.006).[36] Recently, Abufaraj et al performed a meta-analysis of the differential impact of GnRH antagonists and agonists on the clinical safety and oncologic outcomes of patients with metastatic prostate cancer.[37] Results suggested that there was no significant difference in PSA progression between the two groups, but the overall mortality of GnRH antagonists was lower than that of GnRH agonists (RR: 0.48, 95% CI: 0.26–0.90, p=0.02).[37] Of note, the study of Abufaraj et al included more clinical trials based on Klotz et al Both studies supported the short-term overall survival benefit of degarelix, but there are different opinions on its control of PSA.

Relief of Lower Urinary Tract Symptoms and Prostate Volume Reduction

Research on the effects of degarelix on the relief of lower urinary tract symptoms (LUTS) has primarily included three 12-week clinical trials (CS28, CS30, CS31) in non-Asian populations.[38–40] Regarding the reduction in the International Prostate Symptom Score (IPSS), degarelix was superior to goserelin plus bicalutamide in all three studies (Table 1). In the CS28 study, the reduction in IPSS in the full analysis set and per protocol analysis set of the degarelix group was greater than the goserelin group;[39] in the CS30 and CS31 studies, compared to the goserelin group, except for the higher mean IPSS decline in the degarelix group, more patients were reported to have an IPSS decrease >3 points.[38,40] In terms of reducing prostate volume, degarelix also performed better in CS28, but there was no significant difference in CS30 and CS31 compared to goserelin plus bicalutamide.[38–40] Mason et al conducted a pooled analysis of data from the above three clinical trials and concluded that degarelix did show better efficacy in relieving lower urinary tract symptoms in patients with prostate cancer,[41] and this advantage may be because degarelix directly inhibits the growth of benign prostatic hyperplasia cells by reducing cell proliferation and increasing apoptosis.[42] At the same time, the short observation time of the experiment is considered to be the primary shortcoming of the above research, and inconsistency between the relief of LUTS symptoms and changes in prostate volume in the results is considered primarily due to differences in the mechanism of action between the two drugs.[41] However, in a phase III clinical study in China, the improvement in IPSS was comparable between the two treatment groups over one year.[34] The difference in the results of the studies in the two regions is due to differences in race or study lengths or selection bias of included patients. Further analysis or more clinical studies are needed to confirm this. However, what we can understand is that the absolute advantage of degarelix in reducing IPSS is still unknown.

Intermittent ADT, Neoadjuvant ADT and Second-Line Hormone Therapy

Related research on degarelix as an intermittent androgen deprivation therapy for prostate cancer patients has reported good tolerability and efficacy.[43] During the withdrawal period, the serum PSA levels are suppressed for a longer period of time, while testosterone levels return to normal, allowing improved sexual function. In a phase II randomised multicentre study of patients with biochemical recurrence after radical treatment of prostate cancer, two groups of patients received intermittent androgen deprivation therapy with degarelix induction therapy for 4 months and 10 months, and no difference was observed in the duration of the off-treatment interval or the rate of testosterone recovery.[44] The above studies indicate that degarelix can be used as a drug for intermittent androgen deprivation therapy, but the optimal induction time needs to be further studied.

Furthermore, a preliminary prospective study evaluated recovery of serum testosterone levels and sexual function in patients with moderate prostate cancer using GnRH

antagonists as neoadjuvant therapy before external radiotherapy and found that in most patients, testosterone levels and sexual function returned to normal within 9 months after the last administration.[45] A retrospective study involving 406 patients suggested that neoadjuvant GnRH antagonists plus low-dose estramustine phosphate improve the pathological results of high-risk prostate cancer patients and reduce the risk of biochemical recurrence, similar to the effect of GnRH agonists.[46] Interestingly, a Phase II, randomised, open-label study found that neoadjuvant degarelix alone, compared to the use of an LHRH agonist and bicalutamide, is associated with higher levels of intratumoural dihydrotestosterone (DHT), despite similar testosterone levels.[47] These unexpected results might suggest that degarelix activates an alternate pathway for de novo androgen synthesis or that bicalutamide has theoretical off-target properties, such as DHT synthesis inhibition or influences DHT glucuronidation.[47]

In addition, a multicentre randomised phase II clinical trial evaluated the efficacy of degarelix as a second-line hormone treatment for prostate cancer. When patients who failed GnRH agonist treatment were switched to degarelix, the 3-month and 12-month effective rates were only 16.7% ~33.3% and 8.8%, respectively.[48] Moreover, the same low response rate to PSA appeared in other studies of the same type,[49,50] indicating that degarelix has limited effect as a second-line hormone therapy option.

Safety and Tolerability

In the above series of studies, the overall incidence of adverse events (AEs) in the degarelix group was similar to that in the GnRH agonist group (shown in Table 2). Most reported AEs were of mild to moderate intensity, and hot flashes were the most common AE.[8,27,34] Apart from the onset of hot flashes being faster on degarelix versus leuprolide, no major differences were observed in the overall pattern of hot flashes between the two groups.[51] In all studies, local injection site allergic reaction (such as pain, erythema, swelling, nodules, etc.) in the degarelix group was significantly higher than in the GnRH agonist group;[8,20,27,34,35] fortunately, most adverse reactions occurred after the first injection, and the incidence decreased for subsequent maintenance doses.[27] However, results of the two pooled analyses suggested that the incidence of musculoskeletal AEs, including back pain, myalgia, arthralgia, spinal column stenosis, and fracture, in the degarelix group was lower than in the GnRH agonist group.[36,37] Furthermore, there were no significant differences in the overall risk of AEs, such as liver enzyme elevation, liver failure, urinary retention, and fatigue,[37] and recipients of GnRH agonists had relatively fewer AEs, such as joint pain, fatigue, decreased libido, hot flashes, chills, hyperhidrosis, erectile dysfunction, back pain, weight gain, malaise, fever, anaemia, constipation, nasopharyngitis, and hypertension.[37]

In a study combining data from six clinical trials, compared to GnRH agonists, patients treated with degarelix had a reduced risk of cardiovascular AEs within 1 year after treatment, while those with a history of cardiovascular disease exhibited more significant benefits,[52] and this advantage was confirmed in a follow-up study in the UK.[53] Margel et al conducted a phase II clinical study in men with prostate cancer and existing cardiovascular disease, and these men were randomised to receive GnRH agonist or antagonist treatment for 1 year to compare the incidence of cardiovascular events.[54] The degarelix group and GnRH agonist group consisted of 41 and 39 participants, respectively; 20% of patients in the GnRH agonist group experienced major cardiovascular and cerebrovascular events, compared to only 3% in the degarelix group ($p = 0.013$).[54] These results seem to be more robust in confirming that degarelix has greater benefits in cardiovascular events for prostate cancer patients who have pre-existing cardiovascular disease. However, a recent epidemiological study involving 120,216 prostate cancer patients showed that the use of GnRH agonists and degarelix both increased the risk of cardiovascular disease, while bicalutamide monotherapy did not occur.[55] Therefore, we think that the cardiovascular risk reduction in patients using degarelix is only relative to that of GnRH agonists, while the exact effect of degarelix on cardiovascular disease and its mechanism needs to be further studied.

Quality of Life Benefits

Lee et al measured health-related quality of life in 610 patients enrolled in the CS21 trial using SF-12 and the European Organisation for Research and Treatment of Cancer quality of life questionnaire-C30. They found that the progression of PSA and musculoskeletal adverse events had the most significant impact on average utility.[56] However, the results in the above studies suggested that degarelix slows the progress of PSA[27,36] and reduces the incidence of musculoskeletal events,[36,37] so it is believed to improve the quality of life of prostate cancer patients.[56]

Relugolix

Phase I and Phase II Clinical Trials

Relugolix is an oral, highly selective GnRH antagonist that needs to be administered once a day, and its effective half-life is approximately 25 hours. In two phase I clinical studies of relugolix, its efficacy, tolerability, and safety were initially verified, and the minimum initial/maintenance dose required to achieve the expected clinical effect was shown to be 320/80 mg.[57,58] In the subsequent phase II clinical trial, the relugolix group was found to be slightly better than the leuprolide group in terms of inhibiting serum testosterone, lowering PSA levels, and reducing the incidence of AEs.[59] In addition, a randomised, open-label, parallel-group phase II trial evaluated the efficacy and safety of relugolix as a neoadjuvant/adjuvant ADT to external beam radiotherapy in patients with localised intermediate-risk prostate cancer.[60] Both relugolix and degarelix yielded rapid reductions in testosterone not seen with GnRH agonists. When serum testosterone was 1.73 nmol/l and 0.7 nmol/l as the castration threshold, the castration rates of the relugolix group at 24 weeks were 95% and 82%, respectively and were 89% and 68% in the degarelix group. In terms of inhibiting PSA and reducing prostate volume, there was no significant difference between the two groups. For the incidence of AEs, the main disadvantage of the degarelix group was the higher incidence of local injection adverse reactions. There were no obvious differences in other adverse reactions, such as hot flashes, cardiovascular events, or musculoskeletal AEs. Moreover, after stopping drug treatment, the relugolix group returned to normal testosterone levels more quickly than the degarelix group. This advantage is related to its pharmacokinetic characteristics as a daily oral therapy.

Phase III Clinical Trial (HERO)

Based on the relugolix phase II clinical trial, multiple countries jointly launched a 48-week multicentre, randomised, open-label, phase III trial; the study primarily consisted of relugolix (120 mg once daily after a single oral loading dose of 360 mg) and leuprolide (22.5 mg [or 11.25 mg in Japan and Taiwan] by injection every 3 months) groups.[15] For the primary endpoint of the trial (cumulative castration rate at 48 weeks), the relugolix group performed slightly better than the leuprolide group (Table 1). On the 4th day, the cumulative castration rate of the relugolix group was 56.0%, and the cumulative castration rate of the relugolix group was 0; on the 15th day, the cumulative castration rate of the relugolix group was 98.7%, and the relugolix group was 12.0%. The cumulative probability of profound castration (serum testosterone <0.7 nmol/l) in the two groups on day 15 was 78.4% and 1.0%, respectively, and the PSA response rates were 79.4% and 19.8%, respectively. At all available time points, inhibition of FSH levels in the relugolix group was better than the leuprolide group. In the subgroup that was followed up for testosterone recovery, 90 days after drug withdrawal, mean testosterone levels in the relugolix and leuprolide groups were 288.4 ng/dl and 58.6 ng/dl, respectively, indicating that patients in the relugolix group returned to normal testosterone levels faster. This advantage suggests that relugolix is more suitable for prostate cancer patients receiving intermittent hormone therapy.

Among all patients, there was no significant difference in the overall incidence of AEs between the two groups (Table 2). The incidence of grade 1 or 2 diarrhoea in the relugolix group was slightly higher than in the leuprolide group; however, the incidence of major cardiovascular AEs in the relugolix group was significantly lower than in the leuprolide group.[15] In patients with a history of cardiovascular disease, the incidence of cardiovascular AEs in the relugolix group was 3.6% (3/84), while that in the leuprolide group was 17.8% (8/45).[15] In conclusion, the above results suggest that relugolix is superior to leuprolide in short-term oncology efficacy and cardiovascular safety.

Conclusions

In the abovementioned clinical studies, compared to GnRH agonists, degarelix has potential advantages in short-term oncology efficacy, cardiovascular AEs, and musculoskeletal AEs; the main disadvantage of degarelix is the high incidence of AEs at the local injection point. The efficacy and safety of relugolix were initially confirmed in phase III clinical studies, and it is expected to become one of the new options for ADT in prostate cancer. However, many of the above conclusions are based on studies with relatively short follow-up times; additional clinical trials with large sample sizes and longer follow-up times are needed to further confirm or refute these views.

Data Sharing Statement

All data are provided in the manuscript from published papers as cited.

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Disclosure

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