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REVIEW

Research development of a new GnRH antagonist (Elagolix) for the treatment of endometriosis: a review of the literature

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Abstract
Purpose Limitated studies have reported the efficacy of GnRH antagonist on endometriosis symptoms. The aim of our study was to review all available trials to investigate the medical treatment of endometriosis with only GnRH antagonists, with special attention to pharmacodynamic activity, safety, and efficacy.
Methods Pub Med and Sciencedirect database were searched using terms of "endometriosis treatment", "GnRH antagonist", and "Elagolix". The search was limited to clinical studies published in English. Title and abstract were screened to identify relevant articles.
Results Five studies covering use of GnRH antagonist were found. A phase 1 study evaluated the safety, pharmacokinetics, and inhibitory effects on gonadotropins and estradiol of single dose and 7 day elagolix administration to healthy premenopausal women; two phase II studies evaluated efficacy in patient with endometriosis. Moreover, there are two Phase III clinical trials just completed.
Conclusion GnRH antagonists may have the advantage of oral administration and lower incidence of adverse events. Currently, only Phase II studies have been published demonstrating promising results in terms of efficacy, safety, and tolerability. From the results of the phase III studies, elagolix may become a valuable addition to the armamentarium of pharmacological agents to treat endometriosis-related pain.

Keywords Endometriosis treatment · GnRH antagonist · Elagolix

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Introduction

Endometriosis is a benign, chronic inflammatory disorder characterized by the presence and growth of endometrial implants outside the uterine cavity. It is estimated to affect 10% of women of reproductive age, up to 50% of women with chronic pelvic pain, and 20–50% of women with infertility [1–5]. It preferentially occurs on pelvic organs and the peritoneum, whereas extra-abdominal endometriosis is rare [3–5].

The etiology is not precisely understood and it is probably multifactorial [5]. The ectopic endometrium usually is responsive to the cyclical fluctuation of ovarian steroids in terms of proliferation, differentiation, and bleeding. It is a relevant clinical disease, since it often causes pain, dysmenorrhea, dyspareunia, non-cyclical pelvic pain, infertility, and bleeding disorders [6–8]. As a chronic disease, it severely affects quality of life as well as sexual and psychological health [9, 10]. Women with endometriosis are at higher risk of developing intrahepatic cholestasis and experiencing an induced labor [11].

Current treatment options for the management of pain associated with endometriosis include medical therapies and surgical interventions. Laparoscopy is the gold standard for the diagnosis and excision of endometriotic lesions. During surgery, the lesions can be biopsied or excised; in fact, histological study represents the definitive

confirmation of the disease. Surgical removal may be considered as a treatment option in case of an ovarian endometrioma greater than 4 cm, but it may result in ovarian reserve damage; however, recent hemostatic techniques seem to prevent a significant reduction of ovarian reserve [12–15]. Transvaginal ultrasonography and magnetic resonance imaging (MRI) allow to accurately diagnose the presence and extent of deep endometriosis and ovarian endometriosis, prior to surgery or in patients wishing to avoid laparoscopy [16].

Patients with endometriosis can be treated at the time of surgery or may receive a pharmacological treatment. Although surgery improves endometriosis-associated pain, quality of life, and sexual function, it can be associated with intestinal, urological, and vascular complications. For this reason, pharmacological therapies represent the first-line management for endometriosis. The choice of therapy depends on several factors: intensity of pain, age of the patient, desire to become pregnant, patient's choice and impact of the disease on work capacity, sexual function, and quality of life. The combined oral contraceptive (COC) pill and progestogens represent the first-line treatment for endometriosis; they can be started empirically without a surgical diagnosis If the first-line therapy does not cause pain relief, laparoscopic diagnostic confirmation may be recommended before starting second-line hormonal treatments that include gonadotropin-releasing hormone (GnRH) agonists (they induce the suppression of the hypothalamic-pituitary-ovary axis) [17–19]. If all these treatments result ineffective, experimental therapies may be considered. Recently, the use of GnRH antagonists in the treatment of endometriosis has been introduced. GnRH antagonists unlike GnRH agonists have a completely different action, because they induce a competitive blockage of the GnRH receptors on the gonadotropic cellular membrane [14].

This review focuses on the research development of an oral, short-acting, nonpeptide, GnRH antagonist that has been demonstrated to suppress ovarian estrogen production in a dose-dependent mechanism.

Materials and methods

A literature research was performed in the PubMed and ScienceDirect database, spanning from 1990 to 2016. The applied search heading included combinations of the following terms: "GnRH antagonist", "endometriosis", and "Elagolix". The search was limited to clinical studies published in English. Title and abstract were screened to identify relevant articles. References and related articles were checked.

Results

Elagolix is a novel gonadotropin-releasing hormone (GnRH) antagonist orally available, which cause the suppression of ovarian estrogen production in women. It is a nonpeptide and short-acting drug. Oral administration and short half-life (~6 h) allow a fast elimination of elagolix from the body if treatment has to be interrupted for any reason [20, 21].

Struthers et al. performed the first-in-human, double-blind, placebo-controlled, single- and multiple-dose study with sequential dose increase. The objective of this study was to evaluate the safety, pharmacokinetics, and inhibitory effects on gonadotropins and estradiol of single dose and 7 days elagolix administration to healthy premenopausal women. Fifty-five healthy, regularly cycling premenopausal women were recruited. Five cohorts of six subjects each received a single dose of elagolix (25, 50, 100, 200, or 400 mg) or placebo (elagolix/placebo = 5:1). An additional three cohorts, each comprising six subjects, received once-daily doses of elagolix (50, 100, or 200 mg) or placebo (elagolix/placebo = 5:1) for 7 days. The final cohort of seven subjects received elagolix (100 mg) or placebo twice daily (elagolix/placebo = 5:2) for 7 days. The first multiple-dose cohort was enrolled after satisfactory safety results were observed for the first three single-dose cohorts. Initial administration was 7 ± 1 day after the onset of menstruation. Antagonist or placebo was administered at 08.00 h after an over-night fast. Blood samples were collected at the indicated timepoints for serum hormone or plasma antagonist measurement. Adverse events (AEs) (including hot flashes) were characterized as mild, moderate, or severe. Elagolix was well tolerated during both the single-dose escalation up to 400 mg and the multiple-dose escalation up to 200 mg once daily (qd) and 100 mg twice daily (bid) for 7 days. There were no clinically significant safety findings across dose groups, between single-dose and multiple-dose cohorts, or between elagolix and placebo treatments. All subjects but one completed the study protocol. Among the single-dose cohorts, the most frequently experienced AEs were headache (4 of 25 mg elagolix and 1 of 5 placebo) and nausea (2 of 25 mg elagolix and 2 of 5 placebo). Among the multiple-dose cohorts of the study, the most frequently experienced AEs overall were headache (15 of 20 elagolix and 3 of 5 placebo), abdominal pain (6 of 20 elagolix and 0 of 5 placebo), and hot flashes. The majority of AEs were reported as mild in intensity and a few as moderate; none was reported as severe.

Elagolix was not associated with the very intense hot flashes that commonly occur with profound E_2 suppression such as is achieved with GnRH agonist depot. Oral administration of Elagolix is followed by a somewhat delayed dose-related suppression of E_2. Because of its rapid

clearance and short plasma residence time (2.5–4.1 h), pituitary suppression is maintained for only a part of the day (25–400 mg) and baseline gonadotropin levels return by 24 h. However, suppression of E_2 is more prolonged at doses of 50 mg and higher. Daily (50–200 mg) or twice daily (100 mg) administration for 7 days during mid-follicular phase results in a prevention of high mid-cycle E_2 levels in most subjects. Overall, the compound was well tolerated and safe [22].

Carr et al. reported the clinical data from the first randomized, double-blind, placebo-controlled trial with these modified Biberoglu and Behrman (B&B) pain scales in patients with surgically confirmed endometriosis. The primary objective of the study was to estimate the efficacy of elagolix for reducing dysmenorrheal, non-menstrual pelvic pain, and dyspareunia using daily pain scales. The duration of the placebo-controlled treatment period (8 weeks) was chosen as the minimum time necessary to assess treatment effect on the primary outcome measure without excessive dropout in the placebo group. The study consisted of up 8 weeks of screening with data collection to establish baseline pain, an 8 week double-blind placebo-controlled treatment period, a 16 week open-label treatment period with all patients receiving elagolix 150 mg once per day, and a 6 week post-treatment follow-up period. After screening, patients were randomized in a 1:1 ratio to receive a daily tablet of elagolix 150 mg or matching placebo, beginning within 2–5 days of their menstrual cycle and continuing for the first 8 weeks of treatment. Patients were randomized using an interactive voice response system (IVRS). During the double-blind period, there were significantly greater mean reductions from baseline to week in dysmenorrheal (-1.13 ± 0.11 vs. -0.37 ± 0.11, $p < 0.0001$), non-menstrual pelvic pain (-0.47 ± 0.07 vs.-0.19 ± 0.07, $p < 0.0066$), and dyspareunia scores (-0.61 ± 0.10 vs. -0.23 ± 0.10, $p = 0.0070$) in the elagolix group compared with placebo. Continued improvements were observed during the open-label treatment regardless of initial treatment allocation. Elagolix treatment was also associated with significant improvements in quality-of-life measures during the double-blind and open-label periods. The most common adverse events occurring with elagolix were nausea, headache, and hot flush, each in 9.9% of patients. Elagolix was well tolerated over 24 weeks of treatment with very few discontinuation due to adverse events. Treatment-related adverse events were generally mild-to-moderate and were consistent with the drug's mechanism of action. In contrast to progestins, there was no irregular uterine bleeding or overall increase in bleeding with the use of elagolix therapy. Elagolix treatment was associated with a low incidence of hot flush and did not modify serum lipids, changes which have been reported with the use of other hormonal therapies. In this study, Elagolix showed an acceptable safety and tolerability profile, as well as the potential to reduce chronic pelvic pain for up to 24 weeks of treatment in women with a history of endometriosis [23, 24].

Diamond et al. evaluated in a randomized, multicenter, double-blind, placebo-controlled, parallel group Phase 2 study the safety and efficacy of elagolix for treating endometriosis-associated pain. A total of 155 women with laparoscopically confirmed endometriosis were randomized to placebo, elagolix 150 mg, or elagolix 250 mg once daily for 12 weeks. Placebo patients were re-randomized to elagolix (150 or 250 mg) and elagolix patients continued their dosing assignment for 12 additional weeks; the primary efficacy measure was changed from baseline in the monthly mean numerical rating scale for pain at week 12. At week 12, the decreases in dysmenorrhea for participants treated with either elagolix dose were significantly larger compared with placebo ($p < 0.05$). A larger decrease in non-menstrual pelvic pain was observed for both elagolix treatments groups, but this did not reach statistical significance. The reductions in monthly mean dysmenorrheal and non-menstrual pelvic pain scores were maintained through weeks 13–24. Dyspareunia reduction was significantly greater for elagolix 150 mg compared with placebo at weeks 8 and 12 ($p = 0.003$ and $p = 0.032$, respectively) and for elagolix 250 mg compared with placebo at weeks 4 and 8 (p 0.039 and $p = 0.008$, respectively). Reduction in dyspareunia scores continued to be observed during weeks 13–24 and was comparable to the reductions observed with elagolix treatment during weeks 1–12. The analgesic use showed a modest decrease from baseline in all treatment group during the first 12 weeks of treatment. The most common AE reported by elagolix treatment groups compared with placebo were: headache (1.9, 9.8, and 7.7% for the placebo; elagolix 150 mg and elagolix 250 mg groups, respectively), nausea (1.9, 9.8, and 5.8%), and anxiety (0, 5.9, and 5.8%). The reduction in bone mineral density (BMD) was much lower than the approximate 3% loss observed with 3 months of treatment with the GnRH agonist, leuprolide acetate. The authors concluded that elagolix demonstrated an acceptable efficacy and safety profile in women with endometriosis-associated pain.

Literature reports the deleterious impact on long-term bone health by GnRH agonists therapy; thus, Carr et al. inquired the effects of elagolix on BMD. The study consisted in a randomized double-blind study, with 24 weeks treatment and 24 weeks post-treatment time, where they assessed the actions of elagolix (150 mg every day or 75 mg twice a day) versus subcutaneous depot medroxyprogesterone acetate (DMPA-SC) 104 mg/0.65 ml (subcutaneous injection at weeks 1 and 12) on BMD, in women with endometriosis-associated pain. Eligible patients were women aged 18–49 years with a laparoscopically documented diagnosis of endometriosis within 7 years of

screening and a total composite pelvic signs and symptoms score (CPSSS, based on a Biberoglu and Behrman scale) ≥6 with a dysmenorrheal score and a non-menstrual pelvic pain score a least moderate (≥2 at screening and baseline and with at least 7 days of electronic diary entries prior randomization). The primary end point was to evaluate the percentage change from baseline in BMD for the spine and femur (total hip) at week 24. Secondary end point was the BMD changes at weeks 12 and 48 and reversibility of changes in BMD following the discontinuation of treatment at weeks 48 and 72. The authors also investigated the changes in the intensity of dysmenorrheal and non-menstrual pelvic pain. All treatments induced minimal mean changes from baseline in BMD at week 24 (elagolix 150 mg: −0.11/−0.47%, elagolix 75 mg: −1.29/−1.2%, and DMPA-SC: 0.99/−1.29% in the spine and total hip, respectively), with similar or less changes at week 48 (post-treatment). Elagolix was associated with improvements in endometriosis-associated pain, assessed with composite pelvic signs and symptoms score (CPSSS) and visual analogic scale, including statistical non-inferiority to DMPA-SC in dysmenorrheal and non-menstrual pelvic pain components of the CPSSS. The most common adverse events (AEs) in elagolix groups were headache, nausea, and nasopharyngitis, whereas the most common AEs in the DMPA-SC group were headache, nausea, upper respiratory tract infection, and mood swings. This study showed that similar to DMPA-SC, elagolix treatment had minimal impact on BMD over a 24-week period and demonstrated similar efficacy on endometriosis-associated pain [25].

Phase III trials are assessing two separate doses of Elagolix (150 mg once daily and 200 mg twice daily) over a 24-week treatment period. The data demonstrate that, compared to placebo at month 3 and month 6, patients treated with Elagolix reported statistically significant reductions in scores for menstrual pain (dysmenorrhea, DYS) and non-menstrual pelvic pain (NMPP) associated with endometriosis as measured by the Daily Assessment of Endometriosis Pain scale. The results were presented at the 72nd American Society for Reproductive Medicine Scientific Congress & Expo (ASRM) in Salt Lake City, as well as additional abstracts [26–30].

The first pivotal Phase 3 trial [Studies 1, (North America)] was a 24-week, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of Elagolix in 871 women, age 18 to 49, with moderate-to-severe endometriosis-associated pain. It was conducted at 175 sites in the United States, Puerto Rico and Canada. An extension study (M12-667) permitted some women to be treated for an additional 6 months with these doses [26, 27].

The second pivotal Phase 3 trial [Studies 2 (Global)] employed the same design as the first pivotal Phase 3 trial was multinational, and included 815 women with moderate-to-severe endometriosis-associated pain across 226 sites in 13 countries (US and 12 ex-US countries). There was equal representation of enrollment from US and Ex-US countries. An extension study (M12-821) permitted some women to be treated for an additional 6 months with these doses. Together, these two Phase 3 pivotal studies evaluated the safety and efficacy of Elagolix in nearly 1700 women with moderate-to-severe endometriosis-associated pain, representing the largest prospective randomized endometriosis trials conducted to date [26, 27].

In studies 1 and 2, respectively, 871 and 815 participants were randomized and treated; 653 (75%) and 631 (77%) completed. In the two studies, both doses of Elagolix administered orally demonstrated a statistically significant ($p < 0.001$) improvement versus placebo in the percentage of DYS and NMPP responders. In the first study, at month 3, 46% of patients treated with 150 mg once daily and 76% of patients treated with 200 mg twice daily of Elagolix were classified as DYS responders, versus 20% of patients in the placebo group. Fifty percent of patients treated with 150 mg once daily and 55% of patients treated with 200 mg twice daily of Elagolix were classified as NMPP responders, versus 36% of patients in the placebo group. The second pivotal Phase 3 study demonstrated similar results [26, 27].

The safety profile of Elagolix was consistent across both Phase 3 trials and also consistent with prior Elagolix studies. In the first study, the most frequently reported adverse events (AEs) assessed over 6 months were hot flush (7, 24, and 42% for placebo, 150 mg once daily, and 200 mg twice daily, respectively), headache (10, 15, and 17% for placebo, 150 mg once daily and 200 mg twice daily, respectively), and nausea (14, 10, and 16% for placebo, 150 mg once daily and 200 mg twice daily, respectively). As anticipated by its mechanism of action, some AEs, such as hot flush, were dose dependent. The majority of hot flushes (>50%) were mild in severity. Discontinuations due to AEs were 5.9 and 6.1% for placebo in study 1 and study 2, respectively, 6.4 and 4.4% for 150 mg once daily in study 1 and study 2, respectively, and 9 and 10% for 200 mg twice daily in study 1 and study 2, respectively [27].

In both phase 3 studies, [Studies 1 (North America) and 2 (Global)] was evaluated the effect of elagolix on the quality of life (Qol) in women with moderate/severe endometriosis-associated pain (EAP). Over the course of 6 months, treatment with elagolix resulted in significant, dose-dependent improvements in Qol, based on the EHP-30 questionnaire. The Endometriosis Health Profile (EHP-30) is a self-administered questionnaire used to measure health-related Qol. In women with endometriosis [scale of 0 (never) to 4 (always)]. In this study, all five dimensions (pain, control and powerlessness, social support, emotional

well-being, and self-image) of the core component, and 1 (sexual intercourse) from the modular component were assessed at baseline and months 1, 3, and 6 during the treatment period [28].

Studies 1 (North America) and 2 (global) evaluated the effect of elagolix on endometrial morphology and thickness after treatment for 6 months in women with moderate/severe endometriosis-associated pain (EAP). Endometrial biopsies were performed at baseline and months 6 in Study 1, and not in Study 2. Endometrial thickness was measured via transvaginal ultrasound at baseline (day 2–8 menstrual cycle) and at month 6 in both studies. Based on the endometrial biopsies of 867 participants at baseline and 644 at treatment month 6 in Study 1, there was a dose-dependent reduction in proliferative and secretory patterns, an increase in quiescent/minimally stimulated endometrial patterns, and no findings of endometrial hyperplasia after 6 months of treatment with elagolix. There were no adverse endometrial findings in these studies. In women with endometriosis-associated pain (EAP), Elagolix treatment suppressed endometrial proliferation in a dose-dependent manner after 6 months of treatment with no evidence of endometrial hyperplasia, consistent with its mechanism of action [29]. In these studies (Studies 1 and 2), double-blind, randomized, placebo-controlled, multicenter, 6 month, phase 3 studies evaluating two doses of elagolix 150 mg once daily or 200 mg twice daily evaluated the effect of elagolix on bone mineral density (BMD). Participant included in either study was premenopausal, 18–49 years, surgically diagnosed with endometriosis, with a baseline BMD-Z score higher than −1.5. BMD of the lumbar spine, total hip, and femoral neck was measured by dual energy X-ray absorptiometry (DXA) at baseline and month 6 with GE Lunar or Hologic equipment. Compared with baseline, there was a dose-dependent decrease in lumbar spine BMD following 6 months of treatment with elagolix. There were also dose-dependent decreases in BMD of the total hip and femoral neck [30]. After these studies, the FDA could introduce Elagolix in the treatment of endometriosis in 2017 [26–30].

Conclusion

Endometriosis is a chronic disease requiring long-term therapy. The most common symptom is pelvic pain, which presents as dysmenorrhea in the majority of patients with symptomatic endometriosis and also non-menstrual pelvic pain. The choice of medical treatment should be based on efficacy, incidence of adverse events, preference of patients (such as the pattern of uterine bleeding), and cost. Oral contraceptive pill and progestogens allow treating the majority of patients with endometriosis with a satisfactory improvement of pain symptoms, minimal adverse events, and long-term safety [31]. GnRH agonists may be used in patients with symptoms persisting after administration of first-line therapies; however, the long-term treatment with GnRH agonists is associated with frequent hypoestrogenism-related adverse events, and therefore, the combination with an add-back therapy is mandatory [13, 14].

In this scenario, the GnRh antagonist elagolix represents the most intriguing novelty for an actual clinical use in the management of endometriosis. This drug has two main advantages in comparison with the conventional GnRh agonists: the oral formulation and its short half-life (~6 h) that allows for rapid elimination of elagolix from the body if treatment needs to be discontinued for any reason [26–30]. GnRH antagonists may have the advantage of oral administration and lower incidence of adverse events. Phase II studies have been published demonstrating promising results in terms of efficacy, safety, and tolerability [23–25]. The results of phase III trials demonstrate that Elagolix has the potential to be an important treatment option for women suffering from pain related to endometriosis [26–30].

Author contributions Protocol/project development Angioni S, Melis GB. Data collection or management Pontis A, Nappi L. Data analysis Pontis A, Paoletti AM. Manuscript writing Pontis A, Sorrentino F.

Compliance with ethical standards

Conflict of interest Authors declare that have not conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals part performed by any of the authors.

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