NOVEL PHARMACOLOGICAL THERAPIES FOR THE TREATMENT OF ENDOMETRIOSIS

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ABSTRACT

Introduction: Endometriosis is a chronic, estrogen-dependent, inflammatory disease associated with pelvic pain, infertility, impaired sexual function, and psychological suffering. Therefore, tailored patient management appears of primary importance to address specific issues and identify the appropriate treatment for each woman. Over the years, abundant research has been carried out with the objective to find new therapeutic approaches for this multifaceted disease.

Areas covered: This narrative review aims to present the latest advances in the pharmacological management of endometriosis. In particular, the potential role of GnRH antagonists, selective progesterone receptor modulators (SPRMs), and selective estrogen receptors modulators (SERMs) will be discussed. We performed a literature search in PubMed and Embase, and selected the best quality evidence, giving preference to the most recent and definitive original articles and reviews.

Expert opinion: Medical therapy represents the cornerstone of endometriosis management, although few advances have been made in the last decade. Most studies have focused on the evaluation of the efficacy and safety of GnRH antagonists (plus add-back therapy in cases of prolonged treatment), which should be used as second-line treatment options in selected cases (i.e. non-responders to first-line treatments). Further studies are needed to identify the ideal treatment for women with endometriosis.

KEYWORDS: elagolix, endometriosis, GnRH antagonist, linzagolix, relugolix, SPRM, SERM

ARTICLE HIGHLIGHTS

- According to major international guidelines, standard first-line treatments for symptomatic endometriosis include low-dose combined hormonal contraceptives and progestogens, which are effective in about two-thirds of symptomatic women.
- The principal advantages of GnRH antagonists include dose-dependent estrogen suppression, fast reversibility of hormone secretion after the end of the treatment, avoidance of the flare-up effect and oral delivery.
- Oral GnRH antagonists induce dose-dependent symptom amelioration in patients with endometriosis.
- SPRMs have shown promising results in ameliorating endometriosis-associated pain; however, their safety profile regarding potential liver toxicity and progesterone receptor modulator-associated endometrial changes (PAEC) in the endometriotic foci has not been proven with a sufficient level of evidence. The evidence on the potential role of SERMs in treating endometriosis is scarce and of low quality.

1. INTRODUCTION

Endometriosis is a chronic, estrogen-dependent disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and the myometrium, which is usually associated with an inflammatory process [1,2]. Endometriosis affects about 5% of women of reproductive age [3] and lesions could be schematically divided into peritoneal/superficial implants, ovarian endometriotic cysts/endometriomas, deep endometriosis, and extra-abdominal localizations [2]. Endometriosis is associated with painful symptoms such as chronic pelvic pain, dysmenorrhea and dyspareunia, infertility, impaired sexual function, and psychological suffering [4]. In addition, endometriosis is associated with a substantial economic burden, decreased workplace and household productivity [5, 6]. Therefore, given the complex and multifaceted aspects of endometriosis, treatment should be individualized and balanced on the impact of the disease on health-related quality of life [7].

As suggested by the Practice Committee of the American Society for Reproductive Medicine (ASRM), "endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures" [8]. However, patients with endometriosis are extremely heterogeneous both in terms of symptom severity and anatomic abnormalities [1]. In addition, not only the efficacy, but also the safety, the long-term tolerability and the costs of treatments should be taken into account [9]. In particular, long-term adherence to treatment is crucial to guarantee adequate clinical outcomes. In this view, tailored patient management appears of primary importance to address the specific issues and identify the appropriate treatment for each woman [9].

According to major international guidelines, standard first-line treatments for symptomatic endometriosis include low-dose combined hormonal contraceptives (CHCs) and progestogens [8,10,11]. CHCs and progestogens are effective in about two-thirds of women suffering from endometriosis-related pain [1, 12]. However, one-third of patients does not respond, purportedly

due to progesterone resistance [13]. Therefore, there is a need for novel pharmacological approaches to overcome this limit and provide adequate treatment to the whole population of patients with symptomatic endometriosis.

2. METHODS AND MATERIALS

The purpose of this narrative review was to evaluate the role of novel pharmacological therapies in the management of symptomatic endometriosis. We performed a literature search on the electronic databases Pubmed and Embase including all articles published up to July 2022. The following keywords were adopted: endometriosis, treatment, medical therapy, GnRH antagonist, add-back therapy, SPRM, SERM, ulipristal acetate, mifepristone, raloxifene, bazedoxifene. The best quality evidence was selected with preference given to recent and definitive original articles and reviews, robust study designs, high journal impact factor, and high number of citations of individual articles. We focused mainly on clinical studies. The search was limited to full-text articles published in English. Since only de-identified and published data were considered, the current project was exempt from Institutional Review Board approval.

3. GNRH ANTAGONISTS

GnRH antagonists compete with the endogenous decapeptide by binding the GnRH receptors in the anterior pituitary gland, without inducing their activation [14]. Contrarily to GnRH agonists, antagonists do not provoke the initial flare-up phase and cause instead a rapid onset of the therapeutic effect [15]. In addition, GnRH antagonists estrogen suppression in a dose-dependent way, causing a partial suppression when they are administered at lower doses, and an almost complete suppression when taken at higher doses [13]. This tailored suppression represents an important advantage of this class of drugs. In fact, as suggested by Barbieri in his threshold hypothesis [16], partial suppression of estradiol (E2) levels within 30-60 pg/mL could represent the best available compromise between efficacy, tolerance and safety [17]. The achievement of this E2

range is associated with a state of amenorrhea with good control of pain symptoms while maintaining sufficient levels of E2 to prevent the insurgence of typical hypo-estrogenic untoward effects, such as bone mineral density (BMD) loss and vasomotor menopausal symptoms [16]. Other advantages of GnRH antagonists include oral administration as well as the rapid reversibility and prompt recovery of ovarian function after drug discontinuation [13].

On July 24, 2018, the US Food and Drug Administration (FDA) approved Elagolix to manage moderate to severe pain associated with endometriosis [18]. Elagolix has been approved for the management of endometriosis symptoms also in Canada and Israel. In addition, two further oral GnRH antagonists, namely, Relugolix (TAK385) and Linzagolix (OBE-2109), have recently provided encouraging results in randomized phase II and III clinical trials [19-22]. Selected studies are summarized in Table 1.

3.1 ELAGOLIX

Elagolix has a mean plasma half-life that ranges from 2.4 to 6.3 hours and is rapidly absorbed after oral administration [13, 23, 28]. The liver primarily metabolizes elagolix, and 90% of its excretion occurs in the faeces [28].

In 2017, Taylor *et al.* [23] published two double-blind, randomized, placebo-controlled, 6-month phase III trials (Elaris EM-I and Elaris EM-II) to evaluate the efficacy of two different regimens of elagolix (150 mg once daily and 200 mg twice daily). Overall, 872 and 817 women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain were randomized in EM-I and EM-II. About 7 women out of 10 completed the intervention, 653 (74.9%) and 632 (77.4%), respectively. The two co-primary efficacy endpoints were the proportion of women who had a clinical response with respect to dysmenorrhea and the proportion of women who had a clinical response regarding non-menstrual pelvic pain after three months of treatment.

In Elaris EM-I, dysmenorrhea was evaluated at a three month follow-up and the proportions of responders were 46.4% with elagolix 150 mg, 75.8% with elagolix 400 mg, and 19.6% in the placebo group. In Elaris EM-II, corresponding percentages were 43.4% and 72.4% (compared with 22.7% in the placebo group). Regarding the other primary endpoint, i.e. the proportion of responders with respect to non-menstrual pelvic pain, the percentages in Elaris EM-I were 50.4% with elagolix 150 mg and 54.5% with elagolix 400 mg (compared to 36.5% in the placebo group), while in Elaris EM-II the same percentages were 49.8% and 57.8%, as compared to 36.5% in placebo group. The responses, both in terms of dysmenorrhea and non-menstrual pelvic pain, were maintained at six months. Regarding the management of dyspareunia, only women treated with higher doses of elagolix showed a statistically significant reduction compared to placebo after three months of treatment. As expected, reaching a clinically significant amelioration of endometriosis-related pain with elagolix was associated with an improved health-related quality of life and work productivity [29,30]. Moreover, treatment with elagolix was associated with a reduction in fatigue levels [31].

The medium-term effects of treatment with elagolix were evaluated in two phase III extension studies (Elaris EM-III and Elaris EM-IV) [24], in which subjects continued to take elagolix for six additional months. Post-treatment follow-up was up to 12 months. 569 women were recruited for the extension studies (59.7% of the initial participants); therefore, it could be speculated that most of the participants with the worst prognosis (i.e. those who did not respond to, or did not tolerate, elagolix) were excluded [32]. 458 participants completed the extension study while 111 women prematurely abandoned the study. Thus, only 48% (458/952) of the initially recruited participants ended the 12-month treatment period. At time of post-treatment follow-up in EM-III and EM-IV, responder rates for dysmenorrhea were 52.1% and 50.8% with elagolix 150 mg, respectively, and 78.1% and 75.9% with elagolix 400 mg. Responders rates for non-menstrual pelvic pain were 67.8% and 66.4% with elagolix 150 mg, and 69.1% and 67.2% with elagolix 400 mg.

The most frequently reported side effects, in a dose-dependent trend, were vasomotor symptoms (hot flushes). The rate of women reporting hot flushes at a lower dose of elagolix (150 mg daily) was 23.7%, 22.6%, 44% and 36% respectively in Elaris EM-I, -II, -III and -IV. At higher doses (200 mg twice daily), percentages rose to 42.3%, 47.6%, 72% and 77% respectively [23, 24]. Accordingly, the effects of elagolix on BMD were dose-dependent, with a greater decrease of bone density in women receiving higher doses of GnRH antagonist. In particular, at week 52, the mean percent change from baseline in lumbar spine BMD was -3.60 to -3.91% for the high-dose group (200 mg twice daily) [24]. Lastly, 49 pregnancies have been reported during the clinical development program in women taking the drug; therefore, patients should be informed to adopt non-hormonal contraceptive systems during the treatment period to avoid pregnancy [28, 33].

In conclusion, the use of high-dose elagolix was associated with a strong suppression of E2 and a significant improvement in endometriosis-associated pelvic pain, at the cost of increased hypo-estrogenic side effects and a more pronounced decrease in BMD. Conversely, the effect of lower doses of elagolix (150 mg daily) was minor and not associated with a statistically significant reduction in the use of rescue analgesics.

Given this background, the long-term safety of elagolix 400 mg daily plus add-back therapy is currently under investigation (NCT03213457); the objective of this phase III study is to evaluate the potential beneficial effects of add-back therapy (E2 plus norethisterone acetate) associated with elagolix for the mitigation of hypoestrogenic side effects, in particular of BMD loss. A recent report on open-label safety results to 24 months has been recently published [34]. Elagolix 400 mg/d plus add-back therapy for 24 months continues to have a favourable safety profile with minimal long-term effects on BMD [34].

3.2 RELUGOLIX

Relugolix is mainly metabolized by the liver and has a 37-42 hour half-life [35].

Osuga *et al.* [20] published the results of a phase II, multicentre, randomized, double-blind, placebo-controlled study. The safety and efficacy of three doses of relugolix (10 mg, 20 mg and 40 mg) were compared to placebo and subcutaneous leuprorelin. A total of 487 women were enrolled (placebo n = 99; relugolix 10-mg n=103; relugolix 20-mg n=100; relugolix 40-mg n=103; leuprorelin n=82), the treatment period lasted 12 weeks with a 4-week follow-up. Patients who completed the 12-week treatment could enter a 12-week extension study. The mean changes in visual analogue scale (VAS) score for pelvic pain were -3.8 mm in the placebo group; -6.2, -8.1, and -10.4 mm in relugolix 10-mg, 20-mg, and 40-mg groups, respectively; and -10.6 in the leuprorelin group. The results for dyspareunia showed no clear trend of changes with relugolix. Regarding the quality of life assessment, EHP-30 score improved in patients treated with relugolix compared to those under placebo. The incidence of hot-flushes was dose-dependent, varying from 8.7% in the 10-mg group to 52.4 in the 40-mg group; the percentage of women with hot flushes in the higher dose group was greater than that of patients treated with leuprorelin (52.4% vs 41.3%). Accordingly, the decrease in BMD from baseline was also dose-dependent (-1.0% in the relugolix 10-mg group, -1.3% in the relugolix 20-mg group, -2.1% in the relugolix 40-mg group). BMD decrease was similar between relugolix 40-mg and leuprorelin users (-2.1% and -2.2%, respectively). In conclusion, relugolix was superior to placebo and, at higher doses (40-mg), equally effective to leuprorelin for treating pelvic pain associated with endometriosis.

A recent Japanese multicentre phase III randomized study [21] compared the efficacy and safety of 40-mg relugolix with leuprorelin in a 24-week, double-blind trial. Both women with a surgical and clinical diagnosis of endometriosis were deemed eligible; a total of 335 patients were enrolled. The primary endpoint was the change in the maximum VAS score for endometriosis-associated pelvic pain from baseline to the end of treatment; the decrease was comparable between the two study groups (-52.6 ± 1.3 in the relugolix group and -57.5 ± 1.4 in the leuprorelin group). The reduction in dysmenorrhea and non-menstrual pelvic pain VAS scores was similar between the two study groups. As pain improved, the use of analgesics decreased accordingly. On the same line, the

score for Endometriosis Health Profile (EHP-30) and Work Productivity and Activity Impairment Questionnaire improved in both groups in a comparable manner. These results confirmed the non-inferiority of relugolix to leuprorelin. The incidence of adverse events was slightly superior in the GnRH agonist group (90.9% vs 79.5%), and BMD changes from baseline to the end of treatment were comparable (-4.80 % in the relugolix group and -4.84% in the leuprorelin group). Finally, the recovery of serum E2 levels and menstruation occurred earlier after relugolix discontinuation than after leuprorelin. In particular, E2 levels returned within the normal ranges during the 4-week follow-up period in the relugolix group but not in the leuprorelin group. In addition, menstruation returned earlier after relugolix discontinuation (median, 38 days vs 68 days after leuprorelin discontinuation) [21]. Hypothetically, a faster return to normal E2 levels and to the first ovulation could represents an advantage in patients who are planning a pregnancy; however, no data is available on spontaneous pregnancy rates after discontinuation of GnRH antagonists.

In June 2022, two replicate phase 3, multicentre, randomised, double-blind, placebo-controlled studies (namely, SPIRIT 1 and 2) evaluated the efficacy and safety of relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, norethisterone acetate 0.5 mg) in the management of endometriosis-associated pain [27]. Subjects were divided into three groups: placebo, relugolix combination therapy, or delayed relugolix combination therapy (relugolix 40 mg alone in the first 12 weeks followed by relugolix combination therapy in the following 12 weeks). A total of 1261 women were recruited (n=638 SPIRIT 1 and n=623 SPIRIT 2). The co-primary endopoints in both studies were the proportions of responders at the end of the treatment period in terms of dysmenorrhea and non-menstrual pelvic pain relief. The dysmenorrhoea responder rate was substantially higher in the relugolix combination therapy arms than in the placebo arm (75% vs 27% in SPIRIT 1 and 75% vs 30% in SPIRIT 2, both $P < 0.0001$). The differences in the non-menstrual pelvic pain responder rate between the relugolix combination therapy arms and the placebo arm were slightly smaller (59% vs 40% in SPIRIT 1 and 66% vs 43% in SPIRIT 2, both $P < 0.0001$). In patients treated with relugolix combination therapy, mean percentage changes in

lumbar spine and total hip BMD from baseline to week 12 and 24 were less than 1% in both studies. In the delayed relugolix combination therapy group lumbar spine and total hip BMD substantially declined in the first 12 weeks (relugolix monotherapy) and remained stable during the transition to relugolix combined therapy.

3.3 LINZAGOLIX

Linzagolix has a15-18-hour half-life, high oral bioavailability, does not accumulate in the fatty tissue, and lacks of food effects or interactions with CYP3A4 enzymes [13,28,36].

The EDELWEISS trial [22] evaluated the impact of different doses of linzagolix (50 mg, 75 mg, 100 mg, 200 mg) compared to placebo on endometriosis-associated pain in a series of 328 patients. The duration of treatment was 24 weeks. Only women with a surgical diagnosis of endometriosis were deemed eligible. The trial was conducted in 62 centres in the US and in Europe between 2016 and 2017. Percentages of women with a ≥30% reduction in overall pelvic pain (primary efficacy endpoint) at week 12 were 34.5%, 49.4%, 61.5%, 56.4%, and 56.3% in the placebo, 50 mg, 75 mg, 100 mg, and 200 mg groups, respectively. Compared to placebo, the difference was statistically significant for all treated groups except for the 50-mg group (P = .155). On the same line, the percentages of women with a ≥30% reduction in dysmenorrhea and non-menstrual pelvic pain (secondary efficacy endpoints) at week 12 and week 24 were significantly higher for all groups compared to placebo, with the exception of the 50-mg group. Also, a significant reduction in dyspareunia at 12 weeks was reported with the higher dose of linzagolix (200 mg group), but not in the placebo, 50, 75, or 100 mg groups. In addition, a distinct effect of linzagolix was registered in the various domains of the EHP-30 questionnaire. All active dose groups were associated with an improvement in the pain and in the powerlessness domains compared to placebo, whereas only the 200-mg group was related to an amelioration of the other domains (emotional well-being, self-image and social support). The most frequent adverse events were headache and hot-flushes; as expected, vasomotor symptoms were more frequent at higher

doses of linzagolix (42.1% at week 12 for the 200-mg group). Mean percentage (95% CI) BMD changes for lumbar spine from baseline to the end of treatment period were 0.14% (-0.83, 1.11), -0.80% (-1.57, -0.03), -1.0% (-1.71, -0.29), -1.37% (-2.14, -0.59), and -2.60% (-3.56, -1.65) in the 50, 75 fixed-dose, 75 titrated-dose, 100, and 200 mg dose groups, respectively. In particular, in the 200-mg group one woman out of two (52.6%) had a reduction of >3% BMD at week 24.

These results suggest that a daily dose of 75 mg could significantly reduce most endometriosis-associated pain symptoms with minimal BMD changes. Therefore, this dose could be administered without the addition of hormonal add-back therapy. In contrast, high doses (200 mg) are associated with a significant decrease in BMD and would necessitate the addition of add-back therapy for longer-term use [22]. However, longer-term data on safety, in particular with regard to bone mineral density, are required.

3.4 ASP1707

ASP1707 is an oral GnRH antagonist that has been evaluated in a phase II, multicentre, double-blind, randomized, placebo-controlled study [25]. The study was conducted on 540 women in Europe and Japan between 2012 and 2015, of whom 532 received at least a dose of the study drug. Women were allocated into six groups (ASP1707 3 mg n=86; ASP1707 5 mg n=91, ASP1707 10 mg n=90, ASP1707 15 mg n=88, leuprorelin n=89, placebo n=88), and treatment period lasted 24 weeks. The study was divided into two parts (12 weeks each), and subjects randomized in placebo group for Part 1 were also randomized to one of the four ASP1707 doses for Part 2. The leuprorelin group was included to provide a reference for the potential impact of ASP1707 on bone loss. The primary objective was to evaluate the efficacy and the dose-response effect of ASP1707 in decreasing endometriosis-associated pelvic pain.

After 12 weeks of treatment a statistically significant dose-related reduction in numeric rating scale (NRS) for overall pelvic pain ($P = 0.001$), dysmenorrhea ($P < 0.001$), and NMPP ($P = 0.029$)

was observed among ASP1707 doses. Regarding the management of dyspareunia, the change of mean NRS from baseline to end of treatment (Parts 1 and 2) was neither dose dependent nor statistically significant (compared with placebo) at any dosage of ASP1707. Subjects receiving ASP1707 and leuprorelin showed a statistically significant decrease in BMD compared with baseline. In particular, adjusted mean (95% CI) total hip BMD changes from baseline to the end of treatment period (24 weeks) were -0.5 (-0.98, -0.04), -1.3 (-1.8, -0.88), -1.2 (-1.7, -0.71), -1.3 (-1.8, -0.86), and -2.3 (-2.8, -1.8) in the ASP1707 3 mg, 5 mg, 10 mg, 15 mg, and leuprorelin group, respectively. Thus, ASP1707 resulted in a significantly lower BMD loss at end of the treatment period.

4. SELECTIVE PROGESTERONE RECEPTORS MODULATORS (SPRMs)

SPRMs are compounds that bind the progesterone receptor (PR) and have a mixed agonist-antagonist activity. PRs are expressed through two main isoforms: isoform A (PR-A) and isoform B (PR-B), which entail distinct functions depending on the type of cell expressing them [37]. In particular, mifepristone has a higher binding affinity (100%) for the human PR than progesterone (43%) and its metabolites in endometrial and myometrial samples [38, 39]. Mifepristone is able to stimulate PR by inducing dimerization (as A:A, B:B, or A:B); these dimers possess different effects: A:A are functionally silent, A:B can activate transcription, and A:B markedly inhibit transcriptional activation in progesterone responsive cells [39]. Asoprisnil shows a 3-fold higher binding activity to PR than progesterone in the rabbit uterus [39, 40]. In an animal model, large doses of asoprisnil have demonstrated a mixed agonist and antagonist effects [39]. Ulipristal acetate (UPA) shows a significant antagonistic and a partial agonistic effect on PR in humans; when UPA binds to PR, it decreases the binding capacity of endogenous progesterone to its receptor and blocks PR-mediated DNA transcription [39, 41]. In addition, UPA is aslo able to increase the PR isoform ratio of PR-A to PR-B by reducing the level of PR-B receptor and augmenting PR-A expression [39].

In general, SPRMs are able to inhibit ovulation without affecting estradiol secretion; as a consequence, the circulating levels of estradiol remain in the physiological range [33]. In addition, SPRMs inhibit endometrial proliferation, suppress endometrial bleeding, and reduce endometrial production of prostaglandins [33]. Therefore, a potential rationale for using this class of drugs for the treatment of endometriosis appears plausible; however, SPRMs are not used in clinical practice.

In 1996, Kettel *et al*. [42] tested the efficacy of a 6-months course of 50 mg/d of oral mifepristone in nine patients with endometriosis. All the patients reported an improvement in pain symptoms with no hypoestrogenic side effects. During the study period, one patient reported an increase in liver enzymes while receiving treatment. A lower dosage of mifepristone (5 mg/d) was tested two years later [43] on seven patients; women reported a significant improvement in pain symptoms but a suboptimal control of uterine bleeding.

In 2004, a double-blind, placebo-controlled, randomized controlled trial (RCT) on 130 patients with endometriosis evaluated the efficacy of three different oral doses of asoprisnil (5, 10, 25 mg/d for 12-weeks) [44]. All three doses significantly reduced pain symptom scores and provoked amenorrhea in a dose-dependent manner, with no effect on serum estradiol levels. However, as Tosti *et al*. [45] stated, the trials on asoprisnil were interrupted due to the reporting of cases of endometrial hyperplasia.

Apart from their potential hepatic toxicity [46, 47], another grey area related to SPRMs consists in their long-term progesterone antagonist effect on the endometrium, inducing an estrogenic overexposure. SPRMs administration has been associated with specific morphological endometrial changes, including cystically dilatated glands, epithelial distortion, apoptosis, and low mitotic activity in glands and stroma. This specific spectrum of changes is named "progesterone receptor modulator-associated endometrial changes" or PAEC [48]. The potential effects of SPRMs on ectopic endometrium have been evaluated in a recent Canadian study [49]. In 2020, Singh *et al.* [49] published a case series of fifteen women who received UPA prior to surgery over a 27-month

study period. Overall, the mean exposure time to UPA was 5.82 months (range of 2.5-12 months). About seven women out of ten reported being amenorrheic while on UPA. All the 12 patients who reported preoperative pain symptoms reported a significant pain reduction and a complete resolution of symptomatology in one case. Thirteen patients underwent surgical excision of suspected endometriosis, and three cases (21%) showed morphological features similar to PAEC within endometriosis foci. All cases of PAEC-like features in endometriosis also presente with concomitant PAEC in the eutopic endometrium. PAECs appear to be benign and reversible in eutopic endometrium [48]; however, unlike the endometrium that flakes and renews itself through menstruation, intraabdominal endometriosis is unable to do so. Therefore, as suggested by the authors [49], the potential impact of PAECs on endometriosis if left in situ long-term is unknown, and the potential risk of malignant transformation cannot be excluded. Thus, the natural history of PAECs in endometriosis foci will be difficult to assess without exposing patients to repetitive surgical interventions [49]. In conclusion, there is insufficient data to allow definite conclusions on SPRMs' safety and effectiveness [15].

5. SELECTIVE ESTROGEN RECEPTORS MODULATORS (SERMs)

SERMs bind to estrogen receptors (ER-alpha and ER-beta) in target cells, acting as ER agonists in some tissues and as ER antagonists in others [33]. In particular, SERMs have an estrogen-antagonistic effect on endometrial tissue and interact with ERs blocking the hormonal signalling pathway, inducing a reduction in estrogen activity and possibly ameliorating endometriosis-associated pain [50, 51].

Raloxifene (RLX) is a SERM traditionally used to treat osteoporosis. RLX has a beneficial effect on bone density and can reduce the incidence of atherosclerosis without stimulating the endometrium nor the breast in postmenopausal women [52-54]. Therefore, it could be hypothesized that RLX could reduce endometriosis-associated symptoms without impacting on BMD loss, which is associated with a prolonged hypoestrogenic status. Studies on animal models confirmed this

hypothesis demonstrating a regression of endometriotic implants [55,56]. In 2008, Stratton *et al.* [57] performed a randomized, double-blind, placebo-controlled study on 93 women with biopsy-proven endometriosis. Participants were allocated to a placebo or to an active group (oral RLX 180 mg/d) for a six-month period. Unfortunately, the study terminated prematurely because women in the active group reported an earlier pelvic pain relapse and had surgery sooner than those allocated in the placebo group.

Bazedoxifene is another SERM used to treat osteoporosis, which has shown an inhibitory effect on the growth and proliferation of endometrial tissue in a mice model [58]. In another experimental study on a murine model [59], the combination of bazedoxifene and conjugated estrogens (tissue-selective estrogen complex TSEC) decreased endometriotic lesion size compared to controls. TSEC (20 mg of bazedoxifene and 0.45 of conjugated estrogens) was tested for more than 6 months in a patient with stage III endometriosis with resolution of pelvic pain and no adverse effects on the reproductive tract [60]. Furthermore, adding estrogen to bazedoxifene did not stimulate endometrial growth or hyperplasia and did not reduce the efficacy of the SERM [33]. As suggested by Taylor *et al.* [61] bazedoxifene and conjugated estrogens could represent a potential new treatment for endometriosis-associated pain, which is free of the side effects of progestin-based regimens.

In 2018, a Japanese open-label single-arm clinical trial [62] evaluated the effect of SR-16234, a novel SERM, on pain management in ten women with endometriosis and adenomyosis. 40 mg/d of SR-16234 were administered orally for 12-weeks with a statistically significant decrease in pelvic pain symptoms at the end of the treatment compared to baseline values.

6. CONCLUSION

In the last decade, several studies have been performed on various pharmacological medications in order to identify a new treatment option for patients with endometriosis. However, only the GnRH

antagonist elagolix has been approved for market release in some countries as a treatment option for moderate to severe endometriosis-associated pain. In our narrative review, we focused our attention on those classes of drugs which we deem the most promising in the endometriosis field and in the advanced stage of clinical research, particularly GnRH antagonists. However, other hormonal (i.e. dopamine agonists, aromatase inhibitors) and non-hormonal treatments (i.e. statins, metformin, green-tea extract, curcumin, ezetimibe) are under development for endometriosis.

Endometriosis is a chronic disease which profoundly impacts women's lives and as such requires a life-long management plan [8]. Thus, treatments for endometriosis-related pain should be chosen not only considering its efficacy, but also possible side effects, tolerability, adherence to treatment, expense and women's preferences [4]. The goal is to avoid repetitive surgical procedures of doubtful benefit, which may be associated to disease recurrence, complications, and negative impact on ovarian reserve [33, 63, 64]. Given this background, low-dose monophasic CHC and progestogens remain the first-line treatment option in patients with endometriosis, with a potential window for new treatments (i.e. GnRH antagonists) in those who do not respond due to progesterone resistance or when the above medications are not tolerated or contraindicated [32].

On the same line, according to the recently released European Society of Human Reproduction and Embryology (ESHRE) guidelines [10], GnRH antagonists should be prescribed only as a second-line treatment option (for example, if CHCs or progestogens have been ineffective) due to their side-effect profile (including the potential negative impact on BMD). In addition, the ESHRE guidelines [10] underline the limited evidence on dosage and duration of treatment and the need for add-back therapy in cases of prolonged treatment.

Apart from a phase II RCT study comparing Elagolix with subcutaneous depot medroxyprogesterone acetate (MDPA) [65], all the other phase II and phase III trials compared GnRH antagonists with placebo or with GnRH agonists [19-27]. However, MDPA does not represent a first-line treatment option for endometriosis due to its potentially detrimental effect on

BMD in case of prolonged treatment. Thus, future research should focus on pragmatic trials to assess the actual incremental benefit of GnRH antagonists over CHCs or oral progestogens chosen as active comparators [32].

While SPRMs have shown promising results in ameliorating endometriosis-associated pain, their safety profile regarding potential liver toxicity and the presence of PAEC in the endometriotic foci has not allowed sufficient evidence to permit firm conclusions and pose this drug class as a potential treatment option for endometriosis patients. On the same line, the evidence on the potential role of SERMs in treating endometriosis is scarce and of low quality [54], and further research is needed to be able to draw definitive conclusions.

EXPERT OPINION

Medical therapy represents the cornerstone of endometriosis management; however, few advances have been made in the last decade. As a result, most of the studies have focused on evaluating the efficacy and safety of GnRH antagonists.

Principal purported advantages of GnRH antagonists include [13]:

- dose-dependent estrogen suppression, ranging from a partial suppression at lower doses to an almost complete suppression at higher doses
- fast reversibility and return to normal hormone secretion after the end of treatment
- immediate gonadotropin suppression, with avoidance of the flare-up effect
- oral delivery

However, tailoring the levels of hypo-estrogenism may infer the level of clinical response, i.e. a reduction in side effects may be associated with reduced and incomplete pain relief. Available data suggests that low dosages of GnRH antagonists (i.e. dosages that maintain E2 levels in a favourable range to preserve bone density) cannot wholly control endometriosis-associated pain.

The data on oral GnRH antagonists suggest that hormonal add-back is still needed to prevent bone loss and menopausal side effects. Moreover, the flare-up phase could also be prevented using a GnRH agonist [32]. Injecting a depot GnRH agonist during the mid-luteal phase or starting an oral progestogen for 10 days immediately before the GnRH agonist injection can prevent the flare-up phase. Furthermore, the preference for a daily oral pill compared to a trimestral intramuscular injection is subjective [32]. Lastly, a faster return to normal E2 levels and to ovulation could represent an advantage; however, future studies should evaluate this hypothetical beneficial effect in terms of an enhanced pregnancy rate after GnRH antagonists discontinuation compared to GnRH agonists or other first-line drugs. Unfortunately, no data on spontaneous pregnancy rate after GnRH antagonist cessation are available.

GnRH antagonists (plus add-back therapy in cases of prolonged treatment, i.e. > 6 months) could represent a valuable therapeutic option in cases of non-response to first-line treatments (CHCs and progestogens). In general, about one woman out of three does not respond to CHCs and progestogens presumably due to progesterone resistance, and this percentage seems to be higher in patients with deep infiltrating endometriosis [13]. Therefore, as underlined in the recently published ESHRE guidelines [10], GnRH antagonists should be used as second-line treatment options in selected cases.

New ideal treatments for endometriosis should fulfil these characteristics: effective control of pain symptoms (including deep dyspareunia) and cytoreductive effect on endometriotic nodules and localizations. In addition, ideal new drugs should not inhibit ovulation and allow pregnancy seeking during their assumption. Finally, they should have a favourable safety profile and affordable costs so that patients from low-income countries are not excluded from the benefits of novel therapies.

To date, no treatment option with the above profile is available for women with endometriosis. Studies on biologics and nutritional supplements might open new possibilities in this

direction [66]. Moreover, future studies on pharmacological treatment of endometriosis should include a comparison trials with progestogens, as well as being designed as superiority trials [9]. Further studies are needed to identify the ideal drug to treat women with endometriosis.

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TABLE LEGEND

Table 1. Overview of papers evaluating the role of GnRH antagonists for the treatment of endometriosis (literature data 2017-2022).

Table 1. Overview of papers evaluating the role of GnRH antagonists for the treatment of endometriosis (literature data 2017-2022)

Author, year of publication	Study design	N of patients enrolled	Study drug	Comparator	Treatment period	Follow-up period	Primary endpoints	Outcome
Taylor et *al*., 2017[23]	Two double-blind, randomized, placebo-controlled, 6-month phase III trials Elaris EM-I and Elaris EM-II	Women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain were enroled: **Elaris EM-I:** 872, 653 (74.9%) completed the intervention. **Elaris EM-II:** 817, 632 (77.4%) completed the intervention.	Elagolix 150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group)	Placebo	6 months	12 months	The proportion of women who had a clinical response with respect to dysmenorrhea and nonmenstrual pelvic pain after three months of treatment.	**Elaris EM-I:** Amelioration of DYS observed in 46.4% with elagolix 150 mg and 75.8% with elagolix 400 mg, as compared with 19.6% in the placebo group. Reduction of NMPP reported in 50.4% with elagolix 150 mg and 54.5% with elagolix 400 mg compared with 36.5% in the placebo group. **Elaris EM-II:** Corresponding percentages were 43.4% and 72.4% compared with 22.7% in the placebo group for DYS and 49.8% and 57.8%, as compared with 36.5% for NMPP. The responses, both in terms of DYS and NMPP, were maintained at six months.
Surrey et *al*., 2018[24]	Two 6 months, phase 3, randomized, double-blind, extension studies of Elaris EM-I and Elaris EM-II	Pre menopausal women who had received a surgical diagnosis of endometriosis in the previous 10 years and who had	Elagolix 150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group)	Placebo	6 months	Elaris EM-III and Elaris EM-IV provide for a posttreatment follow-up	Medium-term effects of elagolix treatment.	**EM-III:** Responder rates for DYS were 52.1% with elagolix 150 mg, and 78.1% with elagolix 400 mg.

	described previously (Elaris EM-III and Elaris EM-IV)	moderate or severe endometriosis-associated pain: 569 women were recruited for the extension studies (59.7% of the initial participants), 458 (48%) participants completed the extension study.				period of up to 12 months.		Responder rates for NMPP were 67.8% with elagolix 150 mg, and 69.1% with elagolix 400 mg. **EM-IV:** corresponding percentages were 50.8% with elagolix 150 mg, and 75.9% with elagolix 400 mg for DYS and 66.4% with elagolix 150 mg, and 67.2% with elagolix 400 mg. At week 52, the mean percent change from baseline in lumbar spine BMD was -3.60 to -3.91% for the high-dose group (200 mg twice daily).
D'Hooghe *et al*, 2019[25]	Phase II, multicenter, double-blind, randomized, parallel-group, placebo-controlled study (TERRA study)	540 women with moderate-to-severe endometriosis-associated DYS and NMPP, a surgically confirmed diagnosis of endometriosis, and a confirmed regular menstrual cycle of 24–35 days.	ASP1707 3 mg (n = 86); ASP1707 5 mg (n = 91); ASP1707 10 mg (n = 90); ASP1707 15 mg (n = 88)	Placebo (n = 88) or leuprorelin 3.75 mg/month (n = 89)	12 weeks	24 weeks	To determine the efficacy and dose–response relationship of ASP1707 in reducing endometriosis-associated pelvic pain and to assess the safety, tolerability, PK, and the dose–response relationship of ASP1707 in reducing serum E2 levels.	Statistically significant dose-related treatment effects in decreasing in NRS for OPP ($P = 0.001$), DYS ($P < 0.001$), and NMPP ($P = 0.029$) were observed after 12 weeks among ASP1707 doses and were maintained through 24 weeks. Serum E2 and BMD reduced dose dependently with ASP1707 through 24 weeks, however, to a minor degree

								than with leuprorelin.
As-Sanie et *al*., 2020[26]	Multinational, randomized, double-blind, placebo-controlled study	623 premenopausal women with moderate to severe DYS and NMPP	-Relugolix combination-therapy (Rel-CT: relugolix 40 mg with add-back) -Relugolix 40 mg for 12 weeks followed by Rel-CT for 24 weeks	Placebo	12 weeks	24 weeks	Comparison of Rel-CT and placebo on DYS and NMPP at week 24. Responders defined as a reduction of 2,8 points for DYS or 2,1 points for NMPP on the numeric rating scale (NRS).	DYS-reduction: 75.2% in Rel-CT group, 30.4% in placebo group, 72.8 %: in delayed Rel-CT group (72,8%). NMPP-reduction: 66.0% in Rel-CT group, 52.9% in delayed Rel-CT group, 42.6% in placebo group. Adverse effect incidence similar in both the Rel-CT- and placebo-groups. Loss of BMD in Rel-CT group: −0.78%. Rel-CT once daily sign. reduced DYS and NMPP compared to placebo.
Donnez *et al*., 2020[22]	Multinational, parallel- group, randomized, placebo-controlled, double-blind, dose- ranging trial	328 premenopausal women with a surgical diagnosis of endometriosis and moderate to severe endometriosis-associated pain.	50, 75, 100, 200 mg linzagolix	Placebo	24 weeks	24 weeks	Pain reduction of >30% after 12 weeks	Percentages of women with a ≥30% reduction in OPP at week 12 were 34.5%, 49.4%, 61.5%, 56.4%, and 56.3% in the placebo, 50 mg, 75 mg, 100 mg, and 200 mg groups, respectively. Compared to placebo, the

						difference was statistically significant for all treated groups, except for the 50-mg group (P = .155). The percentages of women with a ≥30% reduction in DYS and NMPP at week 12 and week 24 were significantly higher for all groups compared to placebo, with the exception of the 50-mg group. A significant reduction in dyspareunia at 12 weeks with the higher dose of linzagolix (200 mg group) but not with placebo, 50, 75, or 100 mg, was also reported. Mean percentage (95% CI) BMD changes for lumbar spine from baseline to the end of treatment period were 0.14% (-0.83, 1.11), -0.80% (-1.57, -0.03), -1.0% (-1.71, -0.29), -1.37% (-2.14, -0.59), and -2.60% (-3.56, -1.65) in the 50, 75 fixed-dose, 75 titrated-dose, 100, and 200 mg dose groups, respectively.

Osuga *et al*., 2021[19]	Multicentre, randomized, double-blind, placebo-controlled study	487 premenopausal women with diagnosis of endometriosis in the previous 5 years by surgery or magnetic resonance imaging detection of ovarian chocolate cyst DYS and endometriosis related pelvic pain	Relugolix 10 mg (n = 103), 20 mg (n = 100), 40 mg (n = 103)	Placebo (n = 97) or leuprorelin 3.75 mg/month (n = 80)	12 weeks	4 weeks	Change from baseline pelvic pain score during the last month of treatment	Change of pelvic pain (VAS): −3.8 (placebo), −6.2 (10 mg relugolix) - 8.1 (20 mg relugolix), -10.4 (40 mg relugolix); -10.6 (leuprorelin)
Osuga *et al*., 2021[20]	Open-label parallel group, extension trial	397 premenopausal women	Relugolix 10 mg (n = 84), 20 mg (n = 78), 40 mg (n = 89)	Placebo (n = 77); or leuprorelin 3.75 mg (n = 69)	12 weeks	4 weeks	Safety: BMD & treatment-emergent adverse events (TEAEs).	Change in BMD from baseline to week 24: – 0.2% (1.99) (placebo), – 1.6 % (2.34) (10 mg relugolix), – 2.6% (2.94) (20 mg relugolix), – 4.9% (2.91) (40 mg relugolix), – 4.4% (2.16) (leuprorelin)
Harada *et al*., 2022[21]	Phase 3, multicentre, randomized, double-blind, double-dummy, active-controlled study in Japanese patients	335 both women with a surgical and clinical diagnosis of endometriosis	Relugolix 40-mg	Leuprorelin 3.75 or 1.88 mg	24 weeks	4 weeks	The change in the maximum VAS score for endometriosis-associated pelvic pain from baseline to the end of treatment.	The decrease of DYS and NMPP VAS scores were similar between the two study groups (-52.6 ± 1.3 in the relugolix group and -57.5 ± 1.4 in the leuprorelin group). The score for EHP-30 and Work Productivity and AIQ improved in both groups in a comparable manner. BMD changes from baseline to the end of treatment were comparable (-4.80 % in the relugolix

								group and -4.84% in the leuprorelin group).
Giudice *et al*, 2022[27]	Two replicate, phase 3, multicentre, randomised, double-blind, placebo-controlled trials SPIRIT 1, SPIRIT 2 and SPIRIT EXTENSION	Womens with surgically or directly visualised endometriosis with or without histological confirmation, moderate to severe endometriosis-associated pain, DYS and NMPP. -638 premenopausal womens were enrolled into SPIRIT 1: relugolix combination therapy (n=212 of which 181 completed treatment), placebo (n=213 of which 174 completed treatment), or relugolix delayed combination therapy (n=213 of which 182 completed treatment) -623 premenopausal womens were enrolled into SPIRIT 2: relugolix combination therapy (n=208 of which 174	Relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, NETA 0·5 mg), or delayed relugolix combination therapy (relugolix 40 mg monotherapy followed by relugolix combination therapy)	Placebo	24 weeks	4 weeks	The proportion of responders at the end of treatment period in terms of dysmenorrhea and non-menstrual pelvic pain relief.	**In SPIRIT 1**, Treatment difference between relugolix combination group and placebo group for DYS and NMPP responders were 47·6% [95% CI 39·3–56·0]; p<0·0001) and 18·9% [9·5–28·2]; p<0·0001) respectively. **In SPIRIT 2**, Treatment difference between relugolix combination group and placebo group for DYS and NMPP responders were 44·9% [95% CI 36·2–53·5]; p<0·0001) and 23·4% [95% CI 13·9–32·8]; p<0·0001) respectively. Least squares mean percentage change in lumbar spine BMD in the relugolix combination therapy versus placebo groups was –0·70% versus 0·21% in SPIRIT 1 and –

	completed treatment), placebo (n=208 of which 168 completed treatment), or relugolix delayed combination therapy (n=207 of which 165 completed treatment)		0·78% versus 0·02% in SPIRIT 2, and in the delayed relugolix combination group was –2·0% in SPIRIT 1 and –1·9% in SPIRIT 2. Decreases in opioid use were seen in treated patients as compared with placebo.

GnRH= gonadotropin-releasing hormone, DYS = dysmenorrhea, NMPP = non-menstrual pelvic pain, BMD = bone mineral density, PK= pharmacokinetic, NRS= numerical rating scale, Rel-CT = relugolix 40 mg combination therapy with add-back, VAS = visual analogue scale, NETA = Norethisterone acetate, OPP= overall pelvic pain, E2= Estradiol, EHP-30=Endometriosis Health Profile, AIQ= Activity Impairment Questionnaire.