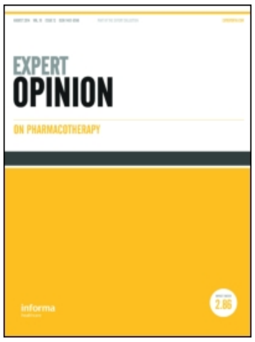

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REVIEW

Current and emerging treatment options for endometriosis

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ABSTRACT

Introduction: Pharmacotherapy has a pivotal role in the management of endometriosis with long-term treatments balancing clinical efficacy (control of pain symptoms and prevention of recurrence of the disease after surgery) with an acceptable safety profile. Treatment choice is based on several factors including age and patient preference, reproductive plans, intensity of pain, severity of disease and incidence of adverse effects.

Areas covered: The aim of this review is to provide the reader with a complete overview of drugs that are currently available or are under investigation for the treatment of endometriosis highlighting on-going clinical trials.

Expert opinion: Almost all of the available treatment options for endometriosis suppress ovarian function and are not curative. Combined oral contraceptives and progestins are commonly administered to these patients in order to ameliorate pain symptoms. Gonadotropin-releasing hormone-agonists are prescribed when first-line therapies are ineffective, not tolerated or contraindicated. Aromatase inhibitors should be reserved only for women who are refractory to other treatments. Amongst the drugs under development, gonadotropin-releasing hormone antagonists have shown the most promising results. Presently, are a number of potential therapies currently in pre-clinical or early clinical studies which may alter treatment strategies in the future although further studies are necessary.

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Endometriosis; combined oral contraceptives; progestins; gonadotropin-releasing hormone agonist; aromatase inhibitors; gonadotropin-releasing hormone antagonist; anti-angiogenetic; anti-oxidant; immunomodulators

1. Introduction

Endometriosis is defined by the presence of endometriotic glands and stroma outside the uterine cavity. Endometriotic lesions may have various locations; they are found more frequently on the pelvic peritoneum, ovaries, and uterosacral ligaments, in the rectovaginal septum and in the vesico-uterine fold, and more rarely in the bowel, diaphragm, umbilicus, pericardium and pleura. Endometriosis may be asymptomatic in some women. However, more frequently, this condition causes pain symptoms (such as dysmenorrhea, deep dyspareunia, non-menstrual pelvic pain, dyschezia) and infertility [1]. Pain is the most debilitating complaint of patients with endometriosis and it negatively affects quality of life, sexual function, working efficiency and social life.

Surgical excision of endometriosis significantly ameliorates pain symptoms [2]; however, it may be associated with complications. Moreover, the recurrence rate of pain symptoms after surgery is not negligible [3]. In addition, in the case of ovarian endometriomas, one concern is the risk of damage to the ovarian reserve [4]. Therefore, medical therapy has a pivotal role in the long-term treatment of endometriosis [5,6]. Current hormonal therapies used to treat endometriosis have no role in improving endometriosis-related infertility [7] and they aim only to alleviate pain symptoms [5]. Thus, these therapies do not definitively 'cure' the disease which may not only persist but may also progress [8] despite the use of endocrine therapies and the improvement of pain symptoms. As a consequence, pain usually recurs when patients discontinue hormonal treatment either because of the adverse effects (AEs) or because of the desire to conceive.

Estradiol (E_2) is of paramount importance in the maintenance of endometriosis. Hormonal therapies currently used to treat endometriosis-related pain primarily acts by suppressing ovulation and, thus, inducing a relatively hypoestrogenic state [6]. First-line hormonal therapies used to treat pain in women with endometriosis are combined with oral contraceptives (COCs) and progestins. The current guidelines recommend an accurate diagnostic workup of women with endometriosis prior to administering second-line hormonal treatments, which include gonadotropin releasing hormone analogues (GnRH-as) or aromatase inhibitors (AIs).

However, since the original description of endometriosis by Sampson [9], our knowledge of the molecular pathways involved in the pathogenesis of the disease has largely increased. Based on these molecular studies, several new drugs have been tested *in vitro* and in animal models of endometriosis [10,11].

A comprehensive literature research was conducted to identify the published studies evaluating the drugs used or

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Article highlights

- Pharmacotherapy plays a pivotal role in the management of patients with endometriosis and long-term treatments should balance clinical efficacy (controlling pain symptoms and preventing recurrence of disease after surgery) with an acceptable safety-profile;
- Combined oral contraceptives and progestins are commonly administered as first-line therapies for the management of endometriosis-associated pain. However, between one-fourth and one-third of patients do not respond to these treatments.
- Gonadotropin-releasing hormone-agonists are prescribed when first-line therapies are ineffective, not tolerated or contraindicated. AIs should be reserved for patients who are refractory to other treatments only in a research environment. It is important to note that all of these drugs have a number of common AEs;
- Almost all of the currently available treatment options for endometriosis suppress ovarian function and are not curative. For this reason, research into new drugs is unsurprisingly demanding. Amongst the drugs currently under investigation, gonadotropin-releasing hormone antagonists, which are currently in late stage clinical development have shown most promise;
- There are a number of potential future therapies currently tested only *in vitro*, in animal models of endometriosis or in early clinical studies with a small sample size. Further studies are necessary to conclude whether these treatments would be of value for the treatment of endometriosis.

This box summarizes key points contained in the article.

under investigation to treat endometriosis. The database of the National Library of Medicine (MEDLINE, 1950–February 2018), EMBASE (1974–February 2018) and the Cochrane Database (February 2018) were used to identify the papers that were published on this topic. The reference lists of all known primary and review articles were examined for additional relevant citations and recent book chapters were reviewed. The database of clinicaltrial.gov was also reviewed to identify ongoing clinical trials.

2. Current therapies for the treatment of endometriosis-related pain

2.1. Non-steroidal anti-inflammatory drugs

Table 1 summarizes the characteristics of main drug classes used for the treatment of endometriosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat endometriosis-related pain symptoms. Surprisingly, there is little evidence to support the use of NSAIDs in the treatment of endometriosis [12]. Tolfenamic acid (200 mg three times per day) [13] and naproxen sodium (275 mg four times per day) [14] have been shown to be superior to placebo for the treatment of dysmenorrhea secondary to endometriosis. Moreover, rofecoxib (25 mg per day) was shown to improve pelvic pain and dyspareunia caused by endometriosis [15], This drug, however, was withdrawn from the market after a study showed an increased cardiovascular risk after long-term use [16]. There is no evidence that one NSAID is more effective than another. Furthermore, patients using in long-term NSAIDs must be aware that these drugs may be responsible significant AEs (such as gastrointestinal ulcers, cardiovascular events, hypertension, and acute renal failure) [12].

2.2. Estroprogestins

Estroprogestins (using oral formulations, vaginal rings or transdermal patches), either sequential or continuous, are commonly administered for treating endometriosis-related pain. They have some practical advantages, including contraception, long-term safety and control of the menstrual cycle [10].

A double-blind, placebo-controlled, multicenter randomized controlled trial (RCT) evaluated the efficacy of cyclic low-dose COC (ethinylestradiol [EE] 0.035 mg and norethindrone acetate [NETA] 1 mg) in comparison to placebo for

Table 1. Current drug class of the treatment of endometriosis.

Drug class	Advantages	Disadvantages
NSAIDs	• First-line therapy • Efficacious in improving moderate women pain symptoms • Not expensive	• They only act on symptoms • Does not block of ovulation
Estroprogestins	• First-line therapy • Not expensive • Low rates of AEs • Multiple route of administration available	• Between one-fourth and one-third of patients treated do not respond to them
Progestins	• First-line therapy • Not expensive • Lower thrombotic risk • Low rates of AEs • Multiple route of administration available	• Only two progestin approved for contraception purpose (DSG, ENG-subdermal implant and LNG-IUS) • Between one-fourth and one-third of patients treated do not respond to them
Gn-RH-as	• Secondary-line therapy (efficacious in treating patients who did not respond to COCs or progestins)	• Not oral administration (subcutaneous) • Expensive • High rate of AEs (estrogen-related)
Danazol	• Not expensive	• Low popularity due to the androgenic AEs
Aromatase inhibitors	• Efficacy in women refractories to other traditional hormonal treatments (should be used only in scientific setting)	• Expensive • High rate of AEs (myalgia, osteoporosis etc.)

GnRH-as = gonadotropin-releasing hormone agonists; GnRH-ant = gonadotropin- releasing hormone antagonists; AE = adverse effect; DSG = desogestrel; ENG = etonorgestrel; levonorgestrel releasing intrauterine device the treatment of pain associated with endometriosis. At its 4-month follow-up, dysmenorrhea improved in patients treated with COC; in contrast, the intensity of chronic pelvic pain did not significantly decrease in both groups [17].

Some RCTs compared COCs to GnRH-as for treating women with endometriosis-associated pain [18,19]. In an open-label RCT, 57 women with laparoscopically diagnosed endometriosis received cyclic low-dose COC (0.02 mg EE and 0.15 mg desogestrel [DSG]) or subcutaneous goserelin (3.6 mg every month) for 6 months. There was a decrease in the intensity of deep dyspareunia in both arms, but the improvement was higher in patients receiving goserelin. A similar decrease in the intensity of chronic pain was observed in both arms. However, six months after the end of the treatment, symptoms recurred without variation in both arms [20]. Another RCT compared the 6-month therapy of COC (EE 0.03 mg and gestoden 0.75 mg) with dietary therapy (vitamins, minerals salts, lactic ferments, fish oil), placebo and intramuscular triptorelin or leuprorelin (LEU, 3.75 mg every month) in women with American Society of Reproductive Medicine stage III-IV endometriosis. After 12 months, women receiving COC or GnRH-as had less severe dysmenorrhea than those receiving placebo or diet. However, both hormonal therapies and dietary supplementation were similarly effective in decreasing the intensity of chronic pelvic pain and dyspareunia [21]. A multicenter RCT compared a COC-based regimen (EE 0.03 mg and gestoden 0.75 mg) for 12 months with triptorelin (3.75 mg intramuscular injection every month) for 4 months followed by the administration of the same COC regimen for a further 8 months. At the 12-month follow-up, both therapies significantly improved dysmenorrhea and chronic pain without inter-group differences [18].

A RCT compared depot medroxyprogesterone acetate (MPA 150-mg dose every 3 months) with continuous COC (EE 0.03 mg and gestoden 0.075 mg daily). After 24 weeks of treatment, there was a greater reduction in dysmenorrhea intensity in the COC group than in the MPA group [22]. Moreover, a recent patient preference study also demonstrated the effectiveness of a 91-day extended cycle COC (levonorgestrel [LNG] plus EE 150/30 µg for 84 days and EE 10 µg for 7 days) for the treatment of endometriosis-related pain [23].

Amongst the other COC-based formulations, no RCT assessed the usefulness of a vaginal ring and transdermal patch for the treatment endometriosis-associated pain. A patient preference prospective cohort study evaluated two sequential estrogen-progestin formulations delivered by a vaginal ring (15 µg EE and 120 µg etonogestrel [ENG], every month) and a transdermal patch (0.60 mg EE and 6.0 mg 17 deacetylnorgestimate every month) for treating recurrent pelvic pain after conservative surgery for endometriosis. Both long-term COC-based regimens succeeded in improving patients' pain, with the ring being more efficacious [24]. Another patient preference study confirmed the efficacy of the vaginal ring (15 µg EE and 120 µg ENG every month) in comparison with continuous oral DSG (75 µg/day) for treating pain in patients with deep infiltrating endometriosis [25].

2.3. Progestins

Progestins decrease the frequency and increase the amplitude of pulsatile gonadotropin-releasing hormone (GnRH) in the hypothalamus, thus decreasinf the secretion of follicle stimulating hormone and luteinizing hormone. As a consequence, the continuous administration of progestins suppresses ovarian steroidogenesis causing anovulation and decreases circulating levels of ovarian hormones. The hypoestrogenism induced by these drugs causes decidualization of both eutopic and ectopic endometrium. Moreover, the association between changes in cytokine mRNA expression and nuclear receptors protein expression in response to progestins therapy may suggest a direct anti-inflammatory effect [26].

Progestins can be classified according their chemical structure in 17-hydroxyprogesterone derivatives and in 19-nortestosterone derivatives [6,27]. Several progestins are available for the treatment of endometriosis including: NETA, CPA, MPA, DSG, ETG, LNG and dienogest (DNG). Progestins can be administered by different routes: orally, by depot subcutaneous injection, by subdermal implant or by intrauterine device. Currently, only depot MPA and NETA as monotherapies are approved by the Food and Drug Administration for the treatment of endometriosis [28].

Progestins are particular efficacious in women suffering dysmenorrhea and menstrual-related symptoms. A strength of progestins is that there is less thrombotic risk compared to COCs. Moreover, progestins can be administered to patients suffering migraine with aura and to those suffering migraine without aura in patients of less than 35 years of age, being better tolerated than COCs [29]. A potential disadvantage of progestins in women desiring contraception is that only a few of them (DSG, the ENG-subdermal implant and the LNG-intrauterine device [IUS]) are approved as contraceptives. Progestins have a good long-term tolerability profile with the most frequent AEs caused by these drugs being spotting, breakthrough bleeding, depression, breast tenderness and fluid retention [30].

A Cochrane review published in 2012 (13 RCTs) investigated the use of progestins versus other drugs (placebo, oral or subdermal COCs, danazol, and GnRH-as) for the treatment of endometriosis-related pain. Only MPA (100 mg daily) was found to be more efficacious than the placebo in reducing endometriosis-related symptoms. Moreover, depot administration of progestins was not superior to other treatments (low dose COCs or LEU) in improving patients' symptoms [31].

Several RCTs have shown efficacy with progestins in treating pain associated with endometriosis [32–41]. Furthermore, prospective non-randomized studies have demonstrated that progestins are also efficacious in treating pain and gastrointestinal symptoms in patients with colorectal endometriosis [42], as well as urinary symptoms in patients with bladder endometriosis [43] and ovarian endometriomas [44].

DNG is a new fourth-generation selective progestin with anti-inflammatory proprieties [45,46]. Several RCTs have investigated the efficacy of DNG in treating endometriosis [47]. A systematic review showed DNG (2 mg/day) to be superior to placebo and as effective as GnRH-as in reducing pelvic pain and growth of endometriotic lesions in patients with endometriosis [48]. Morotti et al. investigated the efficacy of DNG in the treatment of women with rectovaginal endometriosis who had persisting pain symptoms during previous treatment with NETA. In this 24-weeks open-label prospective study, DNG was superior to NETA in improving pain and quality of life. The volume of the endometriotic nodules did not significantly change during treatment with DNG. Therefore, this study demonstrated that DNG may be a suitable option for patients suffering symptoms resistant to other progestins (as an alternative to surgery) [49].

2.4. Gonadotropin releasing hormone analogues

Second-line therapies for the treatment of endometriosis include injectable depot formulations of GnRH-as, which are decapeptides that differ from the endogenous GnRH by the substitution of one or several amino acids. These drugs act by suppressing the production and release of gonadotropins by downregulating the pituitary GnRH receptors, and, thus, inhibiting the ovarian production of estrogen. This hypoestrogenism and the subsequent status of amenorrhea induce the regression of endometriotic lesions. However, GnRH-as may also cause several AEs such as the alteration of lipid profile, depression, hot flushes, urogenital atrophy and loss of body mineral density (BMD); this of course limits their long-term use. The intensity of these AEs can be improved by the administration of NETA or low-dose COCs [50].

In 2010, a systematic review and meta-analysis investigated the use of GnRH-as at different doses, regimens and routes of administration, in comparison with other drugs (such as danazol, LNG-IUS, and placebo) for improving endometriosis-related pain symptoms [51]. Forty-one RCTs were evaluated (4935 women). GnRH-as were more efficacious in relieving pain symptoms than no treatment or placebo. Moreover, there was an improvement in the reduction of pain symptoms among patients receiving GnRH-as compared to those receiving danazol, although there was no statistically significant difference for dysmenorrhea between the two groups. Furthermore, there was no statistically significant difference in overall pain improvement between GnRH-as and LNG-IUS.

In general, there is limited evidence in terms of optimal dosage, duration of therapy and route of administration with GnRH-as.

Furthermore, there are no studies which compare GnRH-as and NSAIDs for the treatment of endometriosis-related pain available in the literature. On the other hand, there are several studies comparing GnRH-as with no treatment or placebo. In a RCT by Fedele et al. the study compared a 6-month treatment with intranasal buserelin acetate (1,200 µg/day) with expectant management in infertile patients with endometriosis, demonstrating a significant pain improvement in patients receiving this drug [52].

Four RCTs investigated LEU and triptorelin (3.75 mg every month) versus placebo. These studies showed that GnRH-as are more efficacious in reducing pain symptoms and in improving quality of life of patients with endometriosis than placebo [53–56].

GnRH-as have been compared to almost all of the currently available hormonal treatments used for treating pain associated to endometriosis. Two multicenter RCTs compared subcutaneous depot MPA (104 mg/0.65 mL, every 3 months) to intramuscular LEU (11.25 mg every 3 months) for 6 months [36,37]. Patients had less intense pain symptoms at the end of treatment and after a follow-up of 12 months [36,37]. Two RCTs compared oral DNG (2 mg twice daily) to GnRH-as (buserelin, intranasal 300 µg/day three times daily, and LEU, 3.75 mg every month) in women with endometriosis. In these studies, the severity of women's pain symptoms decreased significantly without inter-group differences [39,40]. Moreover, three RCTs evaluated LNG-IUS in comparison to GnRH-as [57–59]. Two 6-month RCT evaluated LNG-IUS (20 µg/day) and LEU (3.75 mg every 3 months) in women with endometriosis, reporting a significant similar reduction in the intensity of pain symptoms with both regimens [57,58]. In the another RCT which looked at the 24-week treatment with LNG-IUS (20 µg/day) or goserelin acetate (3.6 mg every month) had similar efficacy in improving pelvic pain [59]. No RCT compared GnRH-as versus CPA or NETA for the treatment of endometriosis-related pain.

Vercellini et al. compared the efficacy of low-dose cyclic COC (0.02 mg EE and 0.15 mg DSG, dose increased to 0.03 mg EE if spotting occurred) and subcutaneous goserelin (3.6 mg every month) in 57 patients with endometriosis [20]. After 6 months, the patients had a similar decrease in the intensity of chronic pelvic pain, although the GnRH-a better alleviated of dyspareunia [20]. COCs and GnRH-as were compared for the treatment of endometriosis-associated pain in other two RCTs [18,19].

A Cochrane review including 27 studies comparing GnRH-as versus danazol in patients with endometriosis showed no significant difference between the two treatments in improving dysmenorrhea, deep dyspareunia and non-cyclic pelvic pain [51].

An RCT compared the efficacy of administering either a combination of anastrozole (AZT, 1 mg/day) and goserelin (3.6 mg every month) or goserelin alone (3.6 mg every month) for 6 months after conservative surgery for severe endometriosis. During the 2-year follow-up, AZT in combination with goserelin caused better pain improvement and an increased period of alleviation before its recurrence than GnRH-a alone [60].

Regarding the best length of therapy for GnRH-as, only one study has been performed [61]. In this RCT, women with endometriosis received nafarelin (200 µg twice daily) for 3 months followed by 3 months of placebo or by other 6 months of nafarelin (200 µg twice daily). Pain symptoms similarly decreased by receiving both schedules and they similarly recurred during the 12-month follow-up [61].

Table 2. New investigational drugs for the treatment of endometriosis.

	Class	Drugs
Animal model		
Hormonal targets	Steroid sulfatase	Estradiol-3-*O*-sulfamate
Anti-angiogenic drugs	Anti-VEGF	Bevacizumab
	TKIs	Sunitib, Sorafenib, Pazopanib
	mTOR	Rapamycin, Temsirolimus, Everolimus
Antioxidants drugs	Statins	Endostatin, simvastatin, atorvastatin, rosuvastatin
	Antidiabetic drugs	Metformin, ciglitazone, pioglitazione, rosiglitazone
	Vitamins	Elocalcitol (Vit D), retinoic acid (Vit A)
	Others	α-lipoic acid, ECGC, Xanthohumol
Immunomodulators	Anti TNF-α	Etanercept, TNFRSF1A and c5N
	NfKb inhibitors	IkB protease inhibitor (TPCK), BAY 11–7085, urinary preparation of human chorionic gonadotropin A (hCG-A), pyrrolidinedithiocarbamate (PDTC), costunolide, imiquimod, bentamapimod
	Others	Telmisartan
Phase I-II trials		
Hormonal treatments	SERM	Bezedoxifene, raloxifene
	SPRM	Mifepristone, anoprisnil
Anti-angiogenic drugs	Dopamine agonists	Cabergoline, quinagolide
Antioxidants drugs	Others	Omega-3 fatty acids, N-acetylcysteine, Resveratrol
Immunomodulators	Anti TNF-α	Infliximab
	Others	V-Endo
Epigenetic agents	Histone Deacetylase	Trichostatin A, Valproic acid
Phase III trials		
Hormonal treatment	GnRH-ants	Cetrorelix, elagolix
	Aromatase inhibitors	Anastrozole, letrozole
Immunomodulators	Others	DLBS1442

GnRH-ant = gonadotropin releasing hormone antagonist, SERM = selective estrogens receptor modulator; SPRM = selective progesterone receptor modulator; TNF-α = tumor necrosis factor-α, NFkB = nuclear factor kappa-light-chain-enhancer of activated B cells, VEGF = vascular endothelial growth factor, TKI = tyrosine kinases inhibitors, EGCG = epigallocatechin-3-gallate.

Four trials evaluated whether different routes of administration influenced the efficacy of GnRH-as [62–65]. Three studies evaluated intranasal buserelin in comparison with subcutaneous daily administration [62–64] and one compared intranasal nafarelin with intramuscular LEU [65]. In the comparison between intranasal and subcutaneous or intramuscular administration of these drugs, there was no statistically significant difference between the groups for pelvic pain, deep dyspareunia and dysmenorrhea [62–65].

3. Investigational hormonal therapies

3.1. Aromatase inhibitors

Table 2 summarizes the main pre-clinical and clinical trials of new investigational drug classes for the treatment of endometriosis. Since the late 1990s, laboratory studies have shown that the aromatase P450 is expressed in both the eutopic and ectopic endometrium of patients with endometriosis while it is not detectable in the eutopic endometrium obtained from healthy women and in endometriosis-free peritoneal tissue [66]. These observations prompted several investigators to inhibit this enzyme by using third-generation nonsteroidal (type II) AIs, such as AZT and letrozole, in order to treat endometriosis. When prescribed to women of reproductive age, AIs should be combined with ovarian suppressive agents such as GnRH-as, progestins or COCs [66]. Prospective small-scale studies showed the efficacy of AIs in improving endometriosis-related pain symptoms [44,67–71], intestinal symptoms in patients with colorectal endometriosis [72], urinary symptoms in patients with bladder endometriosis [73], and in decreasing the volume of endometriotic rectovaginal nodules infiltrating the rectum [74] as well as the volume of endometriomas [44] and the extent of laparoscopically visible endometriosis [75]. Furthermore, an RCT showed that, after conservative surgery for endometriosis, the administration of AI combined with GnRH-a for 6 months is more efficacious than GnRH-a monotherapy in increasing the pain-free interval and in decreasing the recurrence rates of pain [60]. Another ongoing phase IV RCT is evaluating the combination of AZT and LEU for preventing of recurrence of endometriosis compared with LEU as a monotherapy (NCT01769781).

The administration of AIs to women of reproductive age is associated with several AEs including hot flashes, weight gain, bone and joint pain, muscle aches, and less frequently mood swings, headache, vaginal spotting, fatigue, dizziness, depression, increase appetite, insomnia, rash and decreased libido [76]. These AEs severely affect the patient’s quality of life and, thus, the oral administration of AIs does not seem to be suitable for the long-term treatment of endometriosis. In line with this, AIs are not licensed for the treatment of endometriosis and they may only be considered in a research environment when all other options have been exhausted [77].

Moreover, studies investigating letrozole and ATZ for the treatment of endometriosis employed the dose established for the treatment of breast cancer. Importantly, a lower dose of AIs may sufficiently inhibit the activity of peripheral aromatase P450 in patients with endometriosis [78]. Based on this background, an intravaginal ring releasing ATZ and LNG has been developed and it is under investigation for the treatment of endometriosis [79,80]. A randomized, double-blind, double-dummy, parallel-group, multicenter phase IIb study (BAY98-7196) including 319 participants is assessing the efficacy and safety of different dose combinations of ATZ (300 µg/d, 600 µg/d; 1050 µg/d) and LNG (40 µg/d) in an intravaginal ring versus placebo and LEU in women with symptomatic endometriosis over a 12-week period (NCT02203331).

3.2. Gonadotropin releasing hormone antagonists

GnRH antagonists (GnRH-ants) have recently been introduced in the treatment of endometriosis. They have some potential advantages over GnRH-as, which may improve the long-term compliance of the patients. Firstly, GnRH-ants do not cause a flare-up effect because they immediately downregulate gonadotropin secretion by competing with the endogenous GnRH for its pituitary receptors. Therefore, the administration of GnRH-ants leads to an immediate decrease in the circulating levels of gonadal steroid hormones [81]. Secondly, GnRH-ants cause a dose dependent suppression of pituitary and ovarian hormones; in particular, while lower doses cause a partial suppression, higher doses are associated with full suppression. Similar to GnRH-as, the activity of GnRH-ants is completely reversible; in fact, normalization of gonadal function occurs within few days after the discontinuation of treatment when the native GnRH concentration exceeds the GnRH-ants concentration at the pituitary receptors [49]. GnRH-ants are available as an injectable formulation and as oral nonpeptide forms.

Cetrorelix is a GnRH-ant available for subcutaneous injections as sterile lyophilized powder for reconstitution with sterile water for injection. After successful results obtained in pre-clinical studies [82,83], cetrorelix (3 mg subcutaneously every week for 2 months) was tested in 15 patients with laparoscopic diagnosis of endometriosis [84]. All patients were symptom-free during the treatment. The most frequently experienced AEs were headache (20%) and irregular bleeding (20%). There was an almost complete lack of AEs related to estrogen withdrawal (such as mood changes, hot flushes, loss of libido, and vaginal dryness). Moreover, during the treatment, serum level of E_2 oscillated around a mean concentration of 50 pg/mL.

Elagolix is an oral GnRH-ant, rapidly bioavailable after oral administration, which causes the swift decrease of gonadotropins and E_2 concentrations [85]. An American phase II, multicenter, double-blind, RCT including 155 women assessed the safety and efficacy of elagolix for treating endometriosis-associated pain [86]. Patients were randomized to placebo or elagolix (150 mg or 250 mg once daily) for 12 weeks. Patients who received elagolix had regular menstrual cycles during treatment but their cycles were prolonged and the number of days of bleeding per cycle was decreased. Moreover, elagolix significantly improved dysmenorrhea and dyspareunia. The most frequently experienced AEs were headache, nausea, anxiety, hot flashes (which had a mild- moderate intensity), small changes in BMD as well as a little breakthrough bleeding or spotting. Another American double-blind multicenter phase II RCT including 252 women with endometriosis-related pain symptoms showed that elagolix (150 mg every day or 75 mg twice a day) and subcutaneous depot MPA (104 mg/0.65 mL subcutaneously at weeks 1 and 12) for 24 weeks caused minimal mean changes from baseline in BMD and in blood concentrations of N-telopeptide (a biomarker used to measure the rate of bone turnover) [87]. Recently, two similar, double-blind, phase III, RCTs (Elaris Endometriosis I and Elaris Endometriosis II) assessed the efficacy of elagolix (150 mg once daily and 200 mg twice daily) for treating endometriosis-related pain symptoms [88]. Elagolix significantly improved dysmenorrhea and non-menstrual pelvic pain; furthermore, it decreased the use of rescue analgesic drugs. The most frequent AEs were hot flushes (which had mild-moderate intensity), headache and nausea. Less frequent AEs were insomnia, mood swings and night sweats. Two ongoing phase III RCTs (NCT03343067 and NCT03213457) are investigating the safety and efficacy of elagolix as a monotherapy and in combination with E_2 and NETA over 24 months for the treatment of moderate to severe endometriosis-related pain.

Relugolix (TAK-385) is a new oral GnRH-ant. A phase II, open-label, RCT including 397 women with endometriosis-associated pain showed that relugolix (10 mg, 20 mg, and 40 mg orally once daily) and LEU for 24 weeks are equally effective in treating pain symptoms [89]. Metrorrhagia, menorrhagia and hot flushes had similar frequency in patients treated with relugolix at 40 mg and in those treated with LEU. An on-going double-blind, placebo-controlled, phase III RCT is testing the efficacy and safety of relugolix (40 mg once-daily) co-administered with either 12 or 24 weeks of low-dose E_2 (1 mg) and NETA (0.5 mg) in women with endometriosis associated pain (NCT03204318).

The efficacy and safety of another GnRH-ant, OBE2109, is currently being investigated in a dose-finding, double-blind, placebo-controlled phase IIb RCT that aims to include 330 women with moderate-to-severe endometriosis associated pain (NCT02778399).

3.3. Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) directly bind to estrogen receptor (ER)-α and/or ER-β in target cells. They have tissue-selective actions, acting as an ER agonist in some tissues and ER antagonist in others. There are three different categories of SERM: triphenylethylene derivatives, benzothiophene derivative and steroidal compounds. Triphenylethylene derivatives (such as tamoxifen) are used to treat breast cancer and they have no role in the treatment of endometriosis because of the endometrial stimulation. In particular, it has been reported that tamoxifen can induce endometriosis in postmenopausal breast cancer patients [90,91]. Benzothiophene derivatives (such as raloxifene) are non-steroidal compounds which have been investigated for the treatment of endometriosis. Raloxifene has been used to treat osteoporosis since 1999. This drug can influence estrogen levels, having a beneficial estrogenic effects on BMD, not stimulating the endometrium and the breast as well as decreasing the incidence of atherosclerosis. In animal models of endometriosis, raloxifene caused a significant regression of endometriotic lesions [83,92]. A RCT compared the efficacy of 6-month treatment with raloxifene (180 mg daily) with a placebo in patients who underwent laparoscopic excision for endometriosis [93]. This study was halted prematurely because the patients treated with raloxifene experienced pain and had a second surgery significantly sooner than those treated with placebo. However, this study did not investigate the molecular mechanism for the failure of raloxifene in treating endometriosis. It has been hypothesized that the partial agonistic activity of raloxifene to ER-α may be a potential reason for the negative effect on endometriosis. Furthermore, since this drug has agonistic activity to the G protein coupled ER (GPR30), it may also enhance hyperalgesia [94].

Bazedoxifene (BZA) is a novel SERM used to treat osteoporosis in postmenopausal women with increased risk of fracture. It effectively antagonizes estrogen-induced uterine endometrial stimulation without countering estrogenic effects in bone or in the central nervous system. These properties make it an attractive candidate for use in the treatment of endometriosis. Furthermore, *in vitro* and animal studies showed that BZA is able to cause regression of endometriotic lesions [95,96], inhibiting estrogen-mediated cell proliferation [95] as well as decreasing stem cell recruitment within the endometriotic lesions [96]. In contrast with these findings, another study investigated the efficacy of BZA as a monotherapy in comparison to conjugated estrogens on ectopic endometrial implants of mice with endometriosis. At the end of therapy, there was no significant difference in the size of the lesions between the two groups [97]. Regardless, the effectiveness of BZA in the treatment of endometriosis-related pain in humans remains to be investigated.

SR-16234 is structurally different from the other SERMs mentioned above: it has ERα antagonistic activity and has a strong affinity with partial agonistic activity to ERβ [98,99]. A recent open-label single arm clinical trial investigated the efficacy and safety of SR-16234 (40 mg once daily for 12 weeks) in 10 patients with dysmenorrhea and pelvic pain associated with endometriosis and adenomyosis [100]. Although this study showed that SR-16234 decreased the intensity of pelvic pain and dysmenorrhea, these preliminary findings have to be confirmed by RCTs with a larger sample size. Moreover, the mechanism of action of SR-16234 in endometriosis remains to be elucidated. Compared with other SERMs (such raloxifene and BZA), SR-16234 seems to be a purer ER-α antagonist and this characteristic may justify its evident effectiveness in the treatment of endometriosis [100].

3.4. Selective progesterone receptor modulators

Selective progesterone receptor modulators (SPRMs) bind to the progesterone receptor to block or modify downstream its signaling. They have pure agonist, antagonist as well as mixed agonist/antagonist activity.

Mifepristone is currently used in clinical practice for the medical termination of pregnancy. A prospective open-label trial assessed the efficacy of mifepristone (100 mg/day for 3 months) for the treatment of endometriosis. All women had amenorrhea during treatment. Moreover, mifepristone caused an improvement in pelvic pain in all subjects without significant changes in the extent of the disease as evaluated by laparoscopy [101].

Recently a double blind RCT including 360 women with laparoscopic diagnosis of endometriosis investigated the effectiveness and safety of oral mifepristone (daily tablet of 2.5, 5 and 10 mg) in comparison with a placebo [102]. Mifepristone at higher doses (5 and 10 mg daily) significantly improved the symptoms compared to mifepristone at a lower dose (2.5 mg) and to placebo. Moreover, 3.4% of the patients treated with mifepristone had a significant increase in the transaminases. The authors concluded that mifepristone at 5 mg was safer and more effective than the other mifepristone doses and placebo. Another recent RCT including 150 patients with endometriosis compared oral gestrinone (2.5 mg twice weekly) and a combined treatment with oral gestrinone (2.5 mg twice weekly) and oral mifepristone (12.5 mg/time once daily). The combined treatment was more efficacious than gestrinone alone in improving dysmenorrhea, dyspareunia and pelvic pain [103].

Among the other SPRMs, asoprisnil has been investigated for the treatment of endometriosis. In a randomized placebo-controlled trial, this drug (5, 10, and 25 mg) caused a greater reduction of endometriosis-related dysmenorrhea compared with a placebo [104]. Ulipristal acetate, largely used for the treatment of uterine fibroids [105], has never been investigated for the treatment of endometriosis.

3.5. New hormonal targets

Endometriotic lesions may aberrantly express enzymes implicated in estrogen biosynthesis [106]; therefore, it is advisable to investigate new compounds acting on these pathways involved in hormone production. Currently, new compounds targeting enzymes involved in hormones synthesis are under early pre-clinical investigation.

In the estrogen production pathway, steroid sulfatase enzyme is responsible for the conversion of E_2 sulfate, estrone sulfate and dehydroepiandrosterone sulfate to their unconjugated forms. These hormones, having a long half-life and being found in high concentrations in blood and tissues, may act as a reservoir for the production of hormonally active estrogen. The mRNA expression of steroid sulfatase is five-fold higher in patients with ovarian endometriomas compared with the endometrium of patients not affected by endometriosis. Thus, this enzyme may contribute to the development of endometriosis, although its precise role when it is overexpressed is not completely elucidated.

The estradiol-3-*O*-sulfamate is an irreversible inhibitor of steroid sulfatase. In a pre-clinical study in mice, the treatment with this new hormonal inhibitor did not modify plasmatic E_2 levels but it inhibited steroid sulfatase activity and increased progesterone receptor expression. More importantly, in the mice, this drug decreased the weight and size of endometriotic lesions [107].

Recent studies demonstrated also a high expression of 17β-hydroxysteroid dehydrogenase enzymes in endometriotic lesions [108]. In particular, the isoform 1 of this enzyme carries out the conversion of estrone to 17β-estradiol, which may enhance inflammation within the endometriotic lesions. The possibility of blocking the synthesis of estrogens by a specific inhibitor of the 17β-hydroxysteroid dehydrogenase-1 has been assessed in tissue lysates obtained from patients with endometriosis. In the majority of analyzed tissue (70%), this inhibitor succeeded in decreasing the production of 17β-estradiol by greater than 85%. Nevertheless, at the moment, other data *in vivo* on the use of these inhibitors are not yet available [108], although the pharmacokinetic and pharmacodynamic results seem to support their used in the near future [109,110].

4. Investigational non-hormonal therapies

4.1. Anti-angiogenetic drugs

Angiogenesis has a pivotal role in the establishment and progression of endometriosis [111]. Therefore, *in vitro* and animal studies have investigated the efficacy of anti-angiogenetic drugs in this setting. Vascular endothelial growth factor (VEGF) is the most important angiogenetic factor in endometriosis [112]. Studies performed in the endometriosis-induced animal model showed that bevacizumab, a recombinant humanized monoclonal antibody against VEGF, inhibited the development of endometriotic lesions [113] by decreasing cell proliferation [113] and increasing apoptosis [113,114]. Tyrosine kinase inhibitors (TKIs) inhibit the catalytic activity of the receptors of tyrosine kinases, such as vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs). After an effective pre-clinical study performed on ectopic mesenchymal stem cells [115], sorafenib was found to be effective in reducing the endometriotic implants of mice without affecting ovarian reserve [116]. Moreover, a reduction of endometriosis score and VEGF levels was also obtained in rats by administering pazopanib and sunitinib [117]. Finally, sunitinib compared with no medication or danazol decreased similarly the volume and the extent of endometriotic implants [118]. Inhibitors of the mammalian target of rapamycin (mTOR), a protein kinase that critically controls cellular growth, proliferation, and survival, have been investigated for treating endometriosis. In animal models, rapamycin inhibited VEGF-induced angiogenesis and decreased the size of endometriotic implants [119]. Moreover, temsirolimus and everolimus, two specific inhibitors of mTOR/AKT, decreased endometriotic cell proliferation both *in vitro* and in mouse models [120,121]. As dopamine and its receptor-2 have a critical role in the regulation of VEGF-mediated growth of implants [122–124], dopamine agonists have been investigated for the treatment of endometriosis [125–127]. In mice, cabergoline and quinagolide decreased the size of endometriotic implants by inhibiting angiogenesis [125]. Currently, an ongoing pilot phase II study is evaluating the efficacy and safety of cabergoline in association with NETA for the treatment of endometriosis-associated pain (NCT02542410). A proof-of-concept study evaluated the efficacy of quinagolide, administered in a titrated manner (25–75 µg/d) for 18–20 weeks, in decreasing the size of peritoneal endometriotic implants in women with endometriosis. This drug induced a decrease by 69.5%. Moreover, at second-look laparoscopy, the histologic study demonstrated tissue degeneration and down-regulation of VEGF/VEGFR −2 expression [127]. Among other anti-angiogenic agents, endostatin, a proteolytic fragment of collagen XVIII, and angiostatin, a proteolytic fragment of plasmin, suppressed the growth of endometriotic implants in mice [128,129]. No data on the use of these drugs in humans is available.

4.2. Antioxidants

Oxidative stress has a pivotal role in promoting the production of inflammatory mediators such as cytokines, reactive oxygen species and prostaglandins (PGs) in endometriotic implants. This observation has led to the investigation of a large variety of antioxidants in pre-clinical and clinical trials [130,131]. An *in vitro* study showed that omega-3 fatty acids decrease the release of inflammatory mediators in endometriotic stromal cells [132]. In a prospective, randomized experimental study performed in rats, the n-3 eicosapentaenoic acid decreased expression of the mRNA of MMPs, IL-1β, interleukin-1r, PGE synthase, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [133]. Another study showed that derivate 12/15–12/15-lipoxygenase-pathway metabolites protected against the development of new endometriotic implants [134]. Moreover, omega-3 polyunsaturated fatty acids caused, in rats, a greater reduction in the size of endometriotic implants in comparison with 1,25-dihydroxyvitamin-D3 [135]. A nonrandomized prospective study evaluated the supplementation of omega-3 fatty acids (800 mg/day for 12 months) in patients with endometriosis after conservative surgery. All women had an improvement of pelvic pain and dyspareunia compared to those receiving placebo [132].

N-acetylcysteine, a widely available antioxidant, downregulates the expression of genes involved in the production of inflammatory proteins [132]. In an observational cohort study, women with endometriosis received N-acetylcysteine (600 mg three times per day, 3 consecutive days per week); the treatment caused a slight reduction in diameter of endometriomas (−1.5 mm) [136].

The antioxidant and anti-inflammatory effects of α-lipoic acid in the treatment of endometriosis were evaluated in a controlled study in rats. The serum total oxidant status and oxidant stress index levels as well as the endometrial implant volumes and serum and peritoneal tumor necrosis factor-α (TNF-α) levels were significantly lower in animals receiving this anti-oxidant [137].

Statins, acting as competitive inhibitors of the 3-hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, exert not only intrinsic antioxidant activity but also anti-proliferative and anti-angiogenic activity when administered at high doses [138]. Among the investigated compounds, simvastatin significantly reduced the proliferation of endometriotic stromal cells, inhibiting their adhesion to collagen fibers [139]. Moreover, when administered (5 or 25 mg/kg/day for 10 days) in nude mice, it caused a dose-dependent reduction in the number and size of endometriotic implants [140]. In preclinical studies on rats, atorvastatin (2.5 mg/kg) induced the regression of endometriotic lesions and decreased peritoneal and endometriotic expression of VEGF and MMP-9 [141].

The anti-inflammatory activity and the modulation of ovarian steroid production by metformin paved the way to its investigation in the treatment of women with endometriosis [142]. In a pre-clinical study, Yilmaz et al. demonstrated a decrease of size and number of endometriotic implants by enhancing the levels of superoxide dismutase and MMP-2 tissue inhibitor and by reducing the levels of VEGF and MMP-9 in rats receiving metformin [143].

The treatment with tosiglitazone, ciglitazone or pioglitazone, which are able to target a high affinity peroxisome proliferator-activated-γ (PPAR-γ), succeeded in inhibiting proliferation and in increasing the apoptosis of endometriotic cells. Moreover, several studies demonstrated that they also caused regression of established experimental endometriotic implants in animals [144–147].

Among other anti-oxidants, elocalcitol (a vitamin D receptor agonist) and all-trans-retinoic acid (the active metabolite of vitamin A) were investigated for the treatment of endometriosis. Using the mouse model of endometriosis, elocalcitol decreased total lesion weight, reducing the adherence of endometriotic cells to collagen and peritoneal inflammation [142]. After the end of a 17-day administration in mice, retinoic acid decreased the number of endometriotic lesions with high vessel density in comparison with controls [148]. In another pre-clinical study, retinoic acid reduced also the volume of established endometriotic lesions [116].

Among natural antioxidants, resveratrol is a polyphenol which exerts a potent anti-inflammatory effect by acting on several mechanisms such as NF-kB. In pre-clinical studies performed in animal models of endometriosis, the supplementation of resveratrol decreased the number and the volume of endometrial implants, the amount of inflammation as well as proliferation and survival of ectopic endometriotic cells [149]. In a small open-label clinical study, 12 patients with endometriosis who previously did not obtain pain relief under COC administration (drospirenone 3 mg and EE 30 μg) received the addition of resveratrol (30 mg/day). These women had a significant decrease in pain scores. In particular, after 2 months of this double therapy, 82% of them had complete resolution of dysmenorrhea and pelvic pain [150]. Nevertheless, these promising results were not confirmed by another trial in which resveratrol, looked at as a monotherapy (40 mg/day), was compared to a COC regimen (LNG 0.15 mg and EE 0.03 mg) [151].

Epigallocatechin-3-gallate (EGCG) is one of the most abundant antioxidant polyphenols contained in green tea [152]. Pre-clinical studies have shown that EGCG is able to reduce the size of endometriotic implants through inhibition of angiogenesis and fibrosis formation, in particular, reducing mRNA levels of tumor growth factor-β (TGF-β) [152–154]. Currently, an ongoing phase II double-blind placebo controlled RCT is evaluating the 3-month pre-surgical administration of green tea extract (400mg, twice per day) for treating patients with endometriosis (NCT02832271).

Xanthohumol is a prenylated flavonoid isolated from hops with anti-inflammatory and anti-angiogenic properties. In a pre-clinical study on BALB/c mice, this drug inhibited the development of peritoneal and mesenteric endometriotic lesions by suppressing VEGF and PI3-K signaling without inducing serious AEs in the reproductive organs of animals [155].

4.3. Immunomodulators

TNF-α, an inflammatory cytokine, contributes to the proliferation of ectopic and eutopic endometrial cells [156,157], inducing multiple signaling pathways, such as the IKKβ complex, and, thus, NF-kB [158]. In baboons, two human recombinant TNF-α antagonists, TNFRSF1A and c5N, demonstrated exerting inhibitory activity on endometriotic lesions without affecting their menstrual cycle [159,160]. Moreover, etanercept, a fusion protein consisting of human recombinant soluble TNF receptor 2 conjugated to a human Fc antibody subunit, was efficacious in reducing the volume and histopathologic scores of rats' implants, decreasing serum levels of VEGF, IL-6 and TNF-α [161–163].

Furthermore, infliximab, a monoclonal antibody directed against TNF-α, after showing promising results in the animal model [164], was investigated in a RCT including 21 women with severe pain due to rectovaginal endometriosis of at least 1 cm in diameter. Contrary to expectations, it did not modify the size or number of endometriotic implants and endometriosis associated pain [165].

Several inhibitors of NF-kB, such as IkB protease inhibitor (TPCK), thalidomide, BAY 11–7085, the urinary preparation human chorionic gonadotropin A (hCG-A), pyrrolidinedithiocarbamate (PDTC), and costunolide, have all been tested *in vitro* and in animal models for the treatment of endometriosis. All these studies showed a reduction in the expression of genes that regulate the production of inflammatory cytokines, extracellular matrix metalloproteinases (MMPs), apoptosis inhibitors and VEGF [166–172].

Telmisartan is a combined blocker of angiotensin II type 1 receptor (AT1R) and activator of peroxisome proliferator-activated receptor (PPAR)-γ [173]. In two pre-clinical studies in mice, telmisartan, used both as a monotherapy and in combination with parecoxib, a COX-2 inhibitor, significantly decreased the volume of peritoneal endometriotic lesions [174]. In particular, in both studies, telmisartan reduced the lesions' microvessel density and the number of Ki67-positive proliferating cells [175,176].

Furthermore, DLBS1442 is a bioactive fraction extracted from the fruit of a native Indonesian plant, which has immunomodulatory and anti-inflammatory proprieties. In mice models, DLBS1442 inhibited angiogenesis and cell migration in a dose-dependent manner [177]. After being investigated in a clinical trial to treat dysmenorrhea [178], an ongoing prospective, randomized, double-blind controlled phase II-III study is testing its efficacy for the treatment of pain in patients with suspected endometriosis (NCT01942122).

A randomized, placebo-controlled, single-blind study assessed the efficacy of imiquimod in the rat model of endometriosis. Its intraperitoneal administration significantly decreased the volume of endometriotic lesions compared to controls [120]. Recently, bentamapimod (AS602801), an inhibitor of c-Jun N-terminal kinase, has been investigated in rats and it was demonstrated to cause regression of endometriotic implants by 48% [179].

Recently, V-Endo, a tableted preparation derived from hydrolyzed, heat-inactivated, pooled blood of women with endometriosis has been investigated for its immune-induced tolerance and anti-inflammatory effect. An ongoing single-arm I-II trial is recruiting patients to test V-Endo for the treatment of endometriosis-related pelvic pain (NCT03340324).

A new investigated target is AKR1C3, a gene that encodes a member of the aldo/keto reductase superfamily, responsible for catalyzing the reduction of several PGs, such as PG-D2, PG-H2 [103]. An ongoing randomized, placebo-controlled, double-blind, dose-response study is assessing the efficacy and safety of different oral doses of BAY1128688, an AKR1C3 antagonist, for the treatment of patients with symptomatic endometriosis over a 12-week treatment period (NCT03373422).

4.4. Epigenetic agents

Epigenetic inhibitors are innovative investigational targets for treating endometriosis [180]. These compounds act generally on histone deacetylases, a family of enzymes that modulate the acetylation status of histones, critical for protein expression and, thus, for cell survival and proliferation [181]. In a pre-clinical study, trichostatin A, a histone deacetylase, had anti-proliferative activity on endometrial stromal cells with more potent and longer lasting effect in comparison with SPRMs and N-acetylcysteine. In particular, this drug reduced the expression of COX-2, causing a subsequent reduction of inflammatory cytokines production [182,183]. In another pre-clinical study, its administration in mice significantly decreased the size of endometriotic implants and improved the response to noxious thermal stimulus [184]. Valproic acid, another potent histone deacetylase inhibitor, was effective in decreasing the size of endometriotic implants of mice, being also well tolerated [185].

5. Conclusion

Endometriosis is a benign chronic hormonal disease that requires a long-term therapy balancing clinical efficacy (control of pain symptoms and prevention of recurrence) with an acceptable safety-profile. The choice of the most appropriate treatment is based on multiple factors including age and preference of the patients, reproductive plans, intensity of pain, severity of disease and incidence of AEs. Currently, research is focusing on finding both new active hormonal and non-hormonal drugs for treating patients with endometriosis.

6. Expert opinion

Almost all of the currently available hormonal drugs for endometriosis are suppressive and not curative; therefore, the relapse of symptoms is common at the discontinuation of the treatment. Furthermore, most of the currently available treatments for endometriosis-associated pain are contraceptive and, thus, they are not suitable for young patients who wish to conceive.

Among the traditional first-line therapies, estroprogestins (administered orally, as transdermal patch or as vaginal ring) and progestins (administered orally, as depot injections, as implants, or by the LNG-IUS) allow for the treatment of the majority of patients with a satisfactory improvement in pain symptoms, minimal AEs, long-term safety as well as low cost [186]. While COCs have been employed for decades as the first-line treatment option for treating patients with symptomatic endometriosis, the use of progestins as a monotherapy is progressively increasing [28]. Currently, it is controversial whether estroprogestins should be preferred to progestins [187,188]. In fact, it has been hypothesized that estroprogestins, which cause supraphysiologic levels of estrogen, may theoretically be responsible for estrogen dominance in the presence of progesterone resistance, leading to endometriosis progression under its use [188].

Abnormal vaginal bleeding is a commonly experienced AE during the long-term administration of continuous COCs and progestins. The bleeding patterns can be related to the ratio of estrogen to progestin contained in COC formulations or in the absence of estrogen when progestins are administered as a monotherapy. Breakthrough bleeding is common in women receiving long-acting progestins, such as depot MPA or LNG-IUS. Moreover, the analysis of the largest available series (271 patients) on NETA (2.5 mg/day) showed that breakthrough bleeding was experienced by 16.6% of patients [28]. However, in the absence of other AEs, the an increase in NETA dosage to 5 mg/day can effectively improve breakthrough bleeding [189]. A pooled analysis on DNG (2 mg/day) demonstrated that an initial increase in the number of bleeding or spotting days and a desynchronized bleeding pattern is usually followed by a progressive reduction in bleeding days during continuous treatment, accompanied by an increase in the amenorrhea rate. Notably, among 332 patients with endometriosis receiving DNG in this analysis, the number of discontinuations due to heavy or irregular bleeding was low (0.6%) [190]. Overall, the compliance with progestin treatment is likely to be enhanced in clinical practice if patients are informed of the potential effects on bleeding, especially at the beginning of treatment. Moreover, modification in their schedule or dosage may help to ameliorate this AE.

Between one-fourth and one-third of women treated with first-line therapies for endometriosis do not have respond to the therapy. The reasons for the failed response to these compounds may be linked to several molecular mechanisms, such as the imbalance of estrogen and receptor subtypes, as well as cell adhesion molecule imbalance [191], which are all factors implicated in progestin resistance with other estrogen-driven diseases. Nevertheless, a definitive conclusion on this topic cannot be drawn. Moreover, at the moment, no biomarkers for estroprogestin and progestin resistance have been validated [192]. Thus, dynamic monitoring of response to progestin therapy for endometriosis is warranted in order to switch the treatment of this resistant population to other medical therapies or to discuss in the proper time the surgical option. More importantly, imaging exams should only be performed only women report a worsening of clinical symptoms, as the progression of the disease might not be correlated with the worsening of clinical symptoms.

GnRH-as are prescribed when first-line therapies are ineffective in ameliorating women' pain, or when they are not tolerated or contraindicated. Although there is a large body of evidence on the efficacy of GnRH-as for treating endometriosis-associated pain, few studies evaluated the best schedules of therapy in terms of dosages and duration. However, the long-term use of GnRH-as is limited by the incidence of hypoestrogenism related AEs (such as vaginal dryness, hot flashes and BMD loss). For this reason, a treatment longer than 6 months with GnRH-as should be usually combined with add-back therapy with COCs or NETA [193].

AIs should be administered only when patients continue to have persistent pain symptoms despite the use of conventional therapies and only in a research setting. To date, the available studies on AIs include only a small number of patients who receive these drugs for a relatively short period of time (maximum 6 months). Neverthless, the reported rate of AEs (such as hot flushing, myalgia, arthralgia) seems to limit their long-term use in clinical practice [76].

The development, maintenance and progression of endometriotic implants depend on the abnormalities of a variety of molecular mechanisms, such as cell proliferation, apoptosis, invasion capacity, immune function and angiogenesis [194]. The growing understanding of the physiopathology of endometriosis has paved the way for discovering novel innovative medical options.

In the last few years, GnRH-ants have been widely studied. Different from GnRH-as, they maintain sufficient circulating E_2 levels in order to avoid vasomotor symptoms or loss of BMD caused by estrogen deprivation. Recently, two multicenter RCT trials have shown the efficacy of elagolix for treating pain associated to endometriosis [88]. However, the most appropriate dose of elagolix (150–200 mg once or twice daily) still remains unclear [195]. Future studies should also assess whether the addition of an add-back therapy may improve the tolerability of elagolix. Moreover, new RCTs are awaited in order to compare the efficacy of elagolix with other medications (COCs, progestins and GnRH-as) that are commonly prescribed to treat endometriosis-related pain.

Up to now, no SERM has been shown to be effective in the treatment of endometriosis. However, future investigations should aim to find new SERMs that act in the modulation of lesions and chronic pelvic pain such as an ER antagonist [196].

It appears advisable to continue investigating innovative compounds which act on enzymes involved in estrogen production. Currently, new drugs blocking steroid sulfatase and 17β-hydroxysteroid dehydrogenase are under early pre-clinical investigation. Interestingly, the first dual inhibitor of these two pathways has been designed and produced, but no *in vitro* study or investigation in animal models of endometriosis has been reported [197]. Overall, more data on safety and efficacy in animals is needed (especially for 17β-hydroxysteroid dehydrogenase inhibitors) before translating their use to humans with endometriosis.

The establishment of vascularization-based approaches in the management of endometriosis still represents a major challenge. For diagnostic purposes, reliable angiogenic biomarker panels exhibiting high sensitivity and specificity have to be identified. Moreover, for therapeutic purposes, novel compounds selectively targeting the vascularization of endometriotic lesions without inducing severe AEs are required [112,198]. In general, these drugs have relevant AEs, and their activity on endometriotic implants present for years at the time of diagnosis with diffuse fibrotic tissue remaining controversial [199].

Among anti-inflammatory drugs, TNF-α blockers have shown to be efficacious in animal studies. No trials in women with endometriosis has been performed, with the exception of that on infliximab that lead to discouraging results [10].

The efficacy of several antioxidants to relieve endometriosis-associated pain and to reduce endometriotic lesions has been assessed in several pre-clinical and some clinical trials but only poor evidence exists to support their clinical application. Nevertheless, metformin and 3-omega fatty acids may continue to be investigated in this setting, as they are not expensive, largely available and they have a good safety-profile.

As aberrant methylation of the progesterone receptor gene seems to have an important role in the process of specific gene silencing in endometriosis [180], histone deacetylase inhibitors have been investigated. Among these drugs, the administration of valproic acid may be particularly interesting because of its good efficacy demonstrated in animal models with endometriosis, and because of its safety-profile, known from its wide use in human. Despite the promising results obtained in a case series of women with adenomyosis treated with valproic acid [200], no trial in patients with endometriosis has been completed. Thus, any potential beneficial activity of this drug has to be yet confirmed [201].

Several pre-clinical studies have shown intriguing findings evaluating new investigational targets for treating endometriosis. However, a careful evaluation for long-lasting efficacy, tolerance and safety of these new drug classes is necessary before they can support or even displace currently available first- and second-line therapies [11].

In the absence of solid clinical data on new targets for endometriosis therapy derived from large RCTs, the introduction of new targeted drugs (except for GnRH-ant) for the treatment of endometriosis is still far to be realized. More clinical trials are mandatory before these therapies may be considered for the treatment of patients with endometriosis.

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