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REVIEW

ENDOMETRIOSIS: CURRENT KNOWLEDGE FROM LAB TO CLINIC

Role of medical treatment of endometriosis

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ABSTRACT

Endometriosis is a chronic benign disease that affects women of reproductive age. Medical therapy is often the first line of management for women with endometriosis in order to ameliorate symptoms or to prevent post-surgical disease recurrence. Currently, there are several medical options for 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. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic inflammatory conditions, being efficacious in relieving primary dysmenorrhea. Combined oral contraceptives and progestins, available for multiple routes of administration, are commonly administered as first-line hormonal therapies. Several studies demonstrated that they succeed in improving pain symptoms in the majority of patients; moreover, they are well tolerated and not expensive. Gonadotropin-releasing hormone-agonists are prescribed when first line therapies are ineffective, not tolerated or contraindicated. Even if these drugs are efficacious in treating women not responding to COCs or progestins, they are not orally available and have a less favorable tolerability profile (needing an appropriate add-back therapy). Because few data are available on long-term efficacy and safety of aromatase inhibitors they should be reserved only for women with symptoms who are refractory to other treatments only in a research environment. 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 have shown most promise, currently in late-stage clinical development. There is 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.

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KEY WORDS: Endometriosis; Therapy; Progestins; Contraceptives, oral; Aromatase inhibitors.

Endometriosis is a hormone-dependent progressive inflammatory disorder that is diagnosed by the presence of endometrial tissue (glands and stroma) outside the uterine cavity. It is estimated to affect 10% of reproductive-aged women and this percentage rise if we look at infertile women, where it reaches nearly 50%.[1] Women who suffer from endometriosis experiment lower quality of life in confront of their healthy counterpart. In fact, this pathology comes with greater levels of depression, anxiety and impaired social function.[1] Moreover, because of its complex nature it can take 6 to 10 years to make a diagnosis; therefore, increasing patients personal and social discomfort.[2] Another important aspect is that endometriosis generate a great financial burden on the healthcare system[3] that makes of primary importance to find cost-effective strategies to manage this disease. Since it is an estrogen-dependent disease, the classical symptom experimented by most of patients is related to cyclical ovarian hormones

fluctuations during the month manifesting as cyclical pelvic pain with menses (dysmenorrhea), but often noncyclic pain is also present as dyspareunia, chronic pelvic pain, dysuria and dyschezia.[4] Severity of pain does not correlate with the amount of endometrial tissue formed and many patient comes at the diagnosis only after a story of unexplained infertility. The pathologic mechanism of intra-pelvic endometriosis is generally accepted as being largely due to Sampson's theory of retrograde menstruation. Extra-pelvic dissemination finds no univocal explanation and different theory have been developed: lymphatic spread, hematogenous dissemination, or metaplastic transformation. In any case, a relevant role in the genesis of pain is thought to be played by immune dysfunction[5] since endometriosis is characterized by a pro-inflammatory environment in the peritoneal cavity. To tailor the appropriate therapy for the patient, the specialist must keep in mind that both the lesions and the pro-inflammatory milieu can be the target for drug therapy. Control of the pain is the main goal of endometriosis treatment because this comes with the improvement of quality of life and the disease burden. In addition, drugs find their application in decreasing surgical interventions, improving postoperative pain control and even achieve disease remission.[6] Since endometriosis is a benign but chronic disease it is of outmost importance to select pharmacotherapies that maximize benefits and minimize side effects. Many societies including American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) suggest empiric therapy before definitive surgical diagnosis.[6] Conventional medical therapy for endometriosis are represented by nonsteroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives (COCs), progestins, gonadotropin-releasing hormone (GnRH) receptor antagonist and agonist and aromatase inhibitors (AIs). First line therapy may be considered with NSAIDs, COCs and progestins that have all demonstrated efficacy, favourable side effect profile.[7] For women that are refractory to first-line therapy, GnRH agonist and AIs may be considered (Table I).

Endometriosis-related pain

Genesis of pain is complex. The pelvis is a highly vascularized and enervated tissue that in patients with endometriosis shows a typical pro-inflammatory dysfunction. It has been found that peritoneal fluid of women with endometriosis is dense of nerve growth factors. This is responsible of neurogenesis that determines an alteration in the amount of sympathetic and sensory nerve fibers within endometriotic tissue with an increased nerve density in endometriotic nodules.[8] Also, inflammatory cells as cytokines and prostaglandins are attracted to ectopic endometrial tissue and participate to the activation of nerve fibers and can trigger themselves other cells to release other inflammatory molecules in a vicious circle.[9] Another mechanism is nerve fiber entrapment within endometriotic nodules, that can lead to cyclical sciatic pain, weakness and even to sensory loss.[10]

Chronic pelvic pain

Chronic pelvic pain management is challenging. Patients may experiment chronic pain syndromes in absence of endometriosis and patients with endometriosis may never develop chronic pain. Besides, medical or surgical strategies are often incapable of completely solve the problem since it has many components and contributors.[8] In fact, patients with endometriosis experiments central sensitization as a consequence of peripheral nervous system activation. The repetitive and protracted activation of sensory fibers from established lesions can propagate central sensitization that persist beyond the initial stimulus. Patients become highly sensitive to painful stimuli because of endometriosis-induced neuroplastic changes in descending pathways. This is the key in understanding phenomena as allodynia, hyperalgesia and referred pain.[11] Another component that must be considered in the genesis of chronic pain is myofascial pain. It is characterized by the presence of trigger points in musculo-skeletal tissue of the pelvis that are thought to contribute to the genesis of dyspareunia, dyschezia and dysuria. Myofascial pain can respond to injection of local anesthetic or botulinum toxin.[10] Opioid should be

TABLE I.—*Main drugs for medical treatment of endometriosis and their mechanism of action.*

Class	Drugs	Treatment	Action
Anti-inflammatory	COX-1 and COX-2 inhibitors	Tolfenamic acid, naproxen sodium, rofecoxib	Direct anti-inflammatory properties
Hormonal treatment	COCs	Different EP combinations	Suppress ovulation Induce hypoestrogenic state
	Progestins	Norethindrone acetate, dienogest, levonorgestrel	Suppress ovulation Induce hypoestrogenic state – suitable for women that cannot assume estrogen
	GnRH agonist	Leuprolide acetate, nafarelin acetate, doserelin, triptorelin	Suppress the production of gonadotropins and inhibit ovarian steroidogenesis
	Androgens	Danazol	Obstacle sexual steroids synthesis, reduces LH and FSH levels
	Aromatase inhibitors	Anastrozole, letrozole	Decrease local enzymatic conversion of androgen into estrogen and induce hypoestrogenism
	GnRH- antagonist	Elagolix, cetrolelix	Bind GnRH receptors, suppressing gonadotropins but maintain sufficient circulating estradiol levels
	SERM	Bezedoxifene, raloxifene	Bind to estrogen receptors
	SPRM	Mifepristone, anoprisnil	Bind to progesterone receptors
Anti-angiogenic drugs	Anti-VEGF	Bevacizumab	Reduce neoangiogenesis and proliferation of endometriotic tissue
	TKIs	Sunitinib, sorafenib, pazopanib	Interfere in the angiogenetic pathway
	mTOR	Rapamycin, temsirolimus, everolimus	Interfere with proliferation and survival of endometriotic cells
	Dopamine agonists	Cabergoline, quinagolide	Play a role in regulation of VEGF-mediated growth of implants
Antioxidant drugs	Statins	Endostatin, simvastatin, atorvastatin, rosuvastatin	Antioxidant, antiproliferative and anti-angiogenetic activity at high dose
	Antidiabetic drugs	Metformin, ciglitazone, pioglitazone, rosiglitazone	Anti-inflammatory activity and modulation of ovarian steroids Target PPAR-γ and inhibit proliferation of endometriotic cells
	Vitamins	Elocalcitol (vitamin D), retinoic acid (vitamin A)	Antioxidant and anti-inflammatory effect
	Other	Omega-3 fatty acids, N-acetylcysteine, α-lipoic acid	Decrease the release of inflammatory mediators
Immunomodulators	Anti TNF-a	Etanercept, infliximab	Inhibit proliferation of ectopic endometrial cells
Epigenetic drugs	Histone deacetylase inhibitors	Trichostatin A, valproic acid	Antiproliferative activity on endometrial stromal cells

avoided for this purpose since they can increase the phenomenon. Psychological approach to the central pain problem can be useful in long-term management of endometriosis related chronic pain.

Medical therapy goal

All the medical solutions for the management of endometriosis should be considered symptomatic rather than curative and pain management should be individualized. The choice for the adequate drug therapy should be led by multiple factors including patient age, patient preference, willing for pregnancy, severity of pain. Other factors that should be considered are treatment cost, the duration, side effect profiles, risks and accessibility. The goal is to reduce pain by decreasing inflammation and hormone production both ovarian and local.[11] Since endometriosis is a chronic disease, it requires continuous treatment, even after surgery. Counsel patients about this point is of paramount importance both before and after surgery. The main purpose of medical treatment should be symptom improvement, reducing or eliminating the need for surgery or prolonging the time between surgeries,[8] being aware that discontinuation of therapy often leads to recurrence. Recurrence rate is variable, ranging from 4-74%.[12]

Non-steroidal anti-inflammatory drugs

NSAIDs have been used for decades for endometriosis-related pain symptoms but they are probably of minimal effectiveness when used alone. There is a lack of high-quality evidence supporting their efficacy or whether any NSAID is more effective than others.[13] Tolfenamic acid (200 mg three times per day) and naproxen sodium (275 mg four times per day) 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. This drug, however, was withdrawn from the market after a study showed an increased cardiovascular risk after long-term use.[14] There is no evidence that one NSAID is more effective than another. Furthermore, patients using in long-term NSAIDs must be aware that their use can lead to unintended adverse effects (such as gastrointestinal ulcers, cardiovascular events, hypertension, and acute renal failure).[14]

Combined oral contraceptives and progestins

Suppression of endogenous estrogen production is the main goal of a successful endometriosis treatment.[12] COCs and progestins are largely considered as first-line therapies. COCs have proven to be effective in reducing dysmenorrhea and size of lesions compared with placebo also in preventing postoperative recurrence.[14] Hormonal therapy acts through induction of a local hypoestrogenic state by suppressing ovulation. Also, a smaller amount of arachidonic acid is converse into prostaglandins due to the resulting amenorrhea or hypomenorrhea, with the result of pain reduction.[8] Continuous administration has proven to reduce dysmenorrhea but has no effect on chronic pelvic pain or dyspareunia.[15] Breakthrough bleeding can be managed by a brief interruption up to 7 days. Progestin-only therapy finds application where estrogens are contraindicated (smokers, older than 35 years, personal risk factor for myocardial infarction, stroke or thromboembolic events) or when COCs therapy fails. Some authors have recently suggested that progestin monotherapy such as norethindrone acetate and dienogest may be superior to COCs and should be considered as first-line approach. This is particularly true in women with rectovaginal and extra-pelvic endometriosis.[16] The continuous use of progestins have proven equally capable of inhibiting ovulation, inducing amenorrhea, improving of pelvic pain and dysmenorrhea without unfavorable estrogenic effects. Progestins act decreasing serum level of ovarian steroids causing decidualization of endometriotic implants and also inhibiting inflammatory pathways and response causing apoptosis of endometriotic cells.[17] Additional proposed mechanisms of action include anovulation, suppression of metalloproteinase-mediated growth and implantation of ectopic endometrium,[18] inhibition of angiogenesis and also immunomodulation.[18] Norethindrone acetate (NETA) and dienogest (DNG) have shown comparable effects.[19] Breakthrough bleeding, that represents the most common side effect, can be improved with 7- or 14-day estrogen assumption. Progestine-only medications come with a series of formulation: oral, intrauterine device, implantable routes. Although levonorgestrel-releasing intrauterine device (LNG-IUD) has not been FDA-approved for endometriosis, it has shown to be effective. Some women can show progesterone resistance due to decreased receptor sensitivity as a result of aberrant gene expression in the eutopic endometrium.[20] DNG is a fourth-generation progestin, which has been increasingly used for endometriosis treatment. It has anti-androgenetic activity and therefore it improves skin-related side effects.[21] It acts well on endometriotic lesions but has a minimal metabolic impact since it shows little androgenic, estrogenic, glucocorticoid or mineralocorticoid activity.[22] DNG inhibits the secretion of cytokines and seems to have both anovulatory and antiproliferative effect.[21] Indeed, it acts through modulation of prostaglandins production and metabolism in a way that results anti-inflammatory. DNG efficacy has been largely assessed in scientific trials and clinical practice. The recommended optimal dosage is 2 mg daily. It has proven to reduce dyspareunia, pelvic pain, dysmenorrhea and premenstrual pain.[23-25] A recent review of eight RCT that in-

cluded 1273 patients with symptomatic endometriosis, showed that 2 mg/day of DNG were superior to placebo in reducing pelvic pain, and were similar to GnRH-a in controlling pain symptoms. DNG also showed tolerable side effects on long term duration therapy.[26] DNG is also included in combination therapy with estradiol valerate (E2V) and ethinyl estradiol (EE), but few studies have evaluated its efficacy for treatment of endometriosis. In a multi-center RCT DNG combined with E2V compared with GnRH-a showed to be equally efficacious in preventing pain recurrence.[25] A recent study also showed that DNG combined with EE led to a statistically significant reduction of endometriosis-associated pelvic pain.[27] Since DNG has greater specificity in binding progesterone receptors (PR), its use is related to less undesirable side effects.[28] At 2 mg/day dosage, DNG is well tolerated, even on long-term use. Its most common side effects include headache, breast discomfort, depressed mood and acne.[29]

GnRH agonists

GnRH agonists (GnRH-a) are available in a variety of administration routes: intramuscular, subcutaneous, intranasal.

The most used compounds are leuprolide acetate, nafarelin avetate, goserelin acetate and triptorelin.

They act through central down-regulation of gonadotropin-releasing hormone (GnRH) receptors at pituitary level, suppressing the production of gonadotropins and therefore inhibiting ovarian steroidogenesis. Within one month of GnRH-a use, circulating estradiol concentrations will be in the menopausal range. Due to higher cost, limited accessibility, hypoestrogenic side effects these medications are usually considered as second line therapy. Since GnRH-a cause initial stimulation of the hypothalamic-pituitary-gonadal axis, they may cause an initial worsening of symptoms (flare-up effect).[30] This can be avoided or prevented by treatment with aromatase inhibitors during the first 7-10 days of therapy[31] or alternatively giving the initial injection in the luteal phase of the cycle. A Cochrane review of 41 studies, on a total of 4,935 women with endometriosis, GnRH-a appeared to be superior to placebo at relieving endometriosis associated pain and also to be as effective as other therapeutical option such as danazol, COCs and LNG-IUS.[32] They are considered to be particularly suitable for women with deep infiltrating endometriosis and extra-pelvic endometriosis and are especially useful for reducing dyspareunia.[33] Long-term use leads to loss of bone density together with hypoestrogenic status that comes with alteration of lipid profile, hot flushes, urogenital atrophy, headaches and depression. For these reasons they should be use no longer than 6 months and is strongly suggested an hormonal add-back therapy (for instance with progestins as NETA or a combination estrogen/progestin) or avoid bone loss and to ease side effects.[7] Add-back therapy does not interfere with the GnRH-a's efficacy for pain symptoms.[34] High-dose NETA (5 mg/*die*) is the most widely used agent and it is approved by the U.S. FDA for treatment of endometriosis-associated pelvic pain in combination with leuprolide.[28] Patients who cannot use hormonal add-back therapy are suitable for nonhormonal alternatives such as herbal remedies, selective serotonin reuptake inhibitors, and serotonin/norepinephrine reuptake inhibitors. Also, decreasing dose of Gn-RH-a or increasing the interval between doses has been shown to be effective.[35, 36] Besides, patients taking GnRH agonists may develop resistance because endometrial ectopic tissue expresses aromatase and produces estradiol itself.[37]

Other agents

Danazol

The observation that hyperandrogenic states induce atrophy of the endometrium has led to the use of androgens in the treatment of endometriosis. Danazol, a derivative of the synthetic steroid ethisterone, is one of these treatments used. The efficacy of danazol is based on its ability to produce a high androgen/low estrogen environment (a pseudo menopause) which results in the atrophy of endometriotic implants and thus an improvement in painful symptoms. Danazol acts by inhibiting the midcycle follicle-stimulating hormone (FSH) and luteinizing hormone

(LH) surges and preventing steroidogenesis in the corpus luteum. This drug was very popular for the treatment of patients with endometriosis during the 1970s and 1980s. Several studies demonstrated no significant difference between danazol and other medications in improvement of pelvic pain, dysmenorrhea, dyspareunia, dyschezia and pain recurrence rates after surgery;[38] however, its administration may be characterized by the occurrence of weight gain, acne, hirsutism and other androgenic adverse effects; also, with the marketing of GnRH-a, the use of danazol declined.[38]

Aromatase inhibitor

Aromatase P450 converts androstenedione and testosterone to estrone and E2.[38] Elevated levels of aromatase mRNA have been found in ectopic endometriotic implants.[39] Aromatase inhibitors (AIs) decrease local enzymatic conversion of androgen into estrogen and induce hypoestrogenism reducing endometrioc implants growth and invasion.[39] Their use is limited by the high incidence of adverse effect. The ESHRE guidelines suggest AIs therapy combined with COCs, progestin or GnRH agonist in women with rectovaginal endometriosis refractory to other therapy.[5] Letrozole is the most studied drug.

GnRH antagonist

They act by binding the pituitary GnRH receptor, suppress gonadotropin. Differently from GnRH-as, they maintain sufficient circulating estradiol (E2) levels and have less side effect related to hypoestrogenic state. Also, they have an immediate onset of action, without flare-up effect.[40] Elagolix is the most investigated GnRH antagonist (GnRH-ant). Its safety and tolerability have been assessed in a study on 55 premenopausal patients. It caused a rapid decline in serum level of gonadotropins and E2.[41] In a phase II trial, elagolix was demonstrated capable of reducing dysmenorrhea and dyspareunia in comparison to placebo, but no significant differences were found for chronic pelvic pain. Also bone mass density was reduced after treatment.[42] Carr *et al*. compared efficacy of elagolix and depot medroxyprogesterone acetate-subcutaneous (DMPA-SC) and found that elagolix has minimal impact on bone mass density and similar efficacy on pain.[43] In a recent publication by Taylor *et al*. results from two phase III trials (Elaris endometriosis I and II) has been reported. Elagolix showed superior to placebo in both studies ($P<0.001$), on the other hand, women receiving elagolix had higher rates of hot flushes, higher levels of serum lipids and a decrease in bone mass density.[44] Cetrolelix has been studied in clinical trial. In a study by Taniguchi *et al*., it demonstrated efficacy in reducing eutopic endometrial stromal cell proliferation by reducing the levels of tumor necrosis factor-a, but ectopic endometrial stromal cell did not respond.[45] A trial by Küpker *et al*. on 15 women with endometriosis, showed improvement of pain during treatment and a lesion regression al laparoscopy in 60% of patients.[46]

Selective estrogen receptor modulators (SERMs)

Selective estrogen receptor modulators directly bind to estrogen receptor a and/or b and determines estrogen- or anti-estrogen-like actions. Bazedoxifene antagonizes estrogen stimulation on endometrial cells, is effective in preventing bone mass density loss and does not cause negative effects on creast or endometrium.[47] Preclinical studies have shown its efficacy in reducing size of endometriotic lesion 41 and recruitment of stem cell to the endometriotic lesions.[48] Also, raloxifene showed similar results in preclinical studies[49] and was tested on 93 women affected by endometriosis. The study was prematurely interrupted because women receiving raloxifene showed a worsening of pain.[50]

Selective progesterone receptor modulators (SPRMs)

This class of medication bind to the progesterone receptor to block or modify its effects. They induce amenorrhea through selective block of endometrial proliferation without systemic effects of estrogen suppression.[51] They determine changes in endometrium that, however, do not seem to be precursors of cancerous lesion and revert within 6 months after discontinuation of therapy.[52] In a prospective trial, mifepristone was

administrated to 16 women with endometriosis. Women showed improvement of pelvic pain but no significant changes in the extent of implants was assessed.[51] Two subsequent studies, on the contrary, showed also regression of the lesions apart from the improving of the symptoms.[53, 54] Since ulipristal acetate has risen the European Medicines Agency (EMA) attention due to its hepatotoxicity, currently, no clinical data on its utilization for the treatment of endometriosis are available.

Adolescent and young adults

Up to 73% of adolescent and young adults with severe and primary dysmenorrhea are diagnosed with endometriosis.[55] Therefore, there is a need for early diagnosis and treatment to prevent complications and preserve fertility. While a long-term therapy comes with significant cost and side effects, many guidelines support empiric therapy with NSAIDs and HT with our surgical confirmation.[5-7] For women that *in-vitro* fertilization is required, a GnRH-a can be used during gonadotropin stimulation to prevent premature LH surge, potentially improving pregnancy rates.[56]

Also, GnRH-a treatment has proven efficacy in treating endometriosis in the presence of endometriomas without consequence on ovarian reserve. On the contrary, surgery seems to have a negative impact on ovarian reserve.[57]

Postmenopausal women

The main concern in symptomatic postmenopausal woman with personal history of endometriosis is related to the potential malignant transformation of lesions. Current data do not suggest delaying treatment with hormone replacement therapy in symptomatic women. The challenge remains in balancing the risk of malignant transformation of endometriotic residual foci with estrogen alone and the increased risk of breast cancer with long-term use of progestins. The risk of malignant transformation appears low, anyway no high-quality data are available to formulate advise that can suite any women[58] and the final decision of therapy must take into account individualized breast cancer risk.

New pharmacological targets

Anti-angiogenetic drugs

Neoangiogenesis is one of the main mechanism involved in the development and growth of endometriotic implants and drugs targeting the angiogenetic pathways represent an interesting field of study.[59] Vascular endothelial growth factor (VEGF) is the most important angiogenetic factor in endometriosis; studies performed in the endometriosis-induced animal model showed that bevacizumab, a recombinant humanized monoclonal antibody against VEGF, inhibited the development of endometriotic lesions by decreasing cell proliferation and increasing apoptosis.[60] Preclinical studies showed encouraging results, demonstrating in the murine model a regression in the endometriotic lesions.[60-62] Tyrosine kinase inhibitors (TKIs) inhibit the catalytic activity of several receptors of factors involved in the angiogenetic pathway (VEGF receptors, platelet-derived growth factor receptors – PDGFRs, stem cell factor receptors – c-KIT).[63] Sorafenib was found to be effective in reducing the endometriotic implants of mice without affecting ovarian reserve.[64] A reduction of endometriosis score and VEGF levels was also achieved in rats by administering pazopanib and sunitinib. Furthermore, sunitinib compared with no medication or danazol decreased similarly the volume and the extent of endometriotic implants.[64, 65] 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. Rapamycin binds to mTOR and in animal models has been able to inhibit VEGF-induced angiogenesis and reduce the size of endometriotic implants.[66] Also temsirolimus and everolimus, two specific inhibitors of mTOR/AKT, showed similar results by decreasing endometriotic cell proliferation, both *in vitro* and in mouse models.[67] Dopamine agonists have been studied for the treatment of endometriosis since dopamine and its receptor-2 play a critical role in the regulation of VEGF-mediated growth of implants.[68] In mice, cabergoline and quinagolide decreased the size of endometriotic implants by inhibiting angiogenesis.[68] A proof-of-concept study evalu-

ated 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.[69] Quinagolide induced a 69.5% reduction in the size of the lesions, with 35% vanishing completely. Moreover, at second-look laparoscopy, the histologic study demonstrated tissue degeneration and down-regulation of VEGF/VEGFR 2 expression. By interfering with angiogenesis, enhancing fibrinolysis, and reducing inflammation, quinagolide may reduce or eliminates peritoneal endometriotic lesions.[69]

Antioxidants drug

As 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, a large variety of antioxidants were investigated in preclinical and clinical trials.[70] An *in-vitro* study omega-3 fatty acids and N-acetylcysteine decrease the release of inflammatory mediators in endometriotic stromal cells;[70] moreover 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 in rats (NF-kB).[70] Omega-3 polyunsaturated fatty acids caused, in rats, a greater reduction in the size of endometriotic implants in comparison with 1,25-dihydroxyvitaminD3.[71] In a nonrandomized prospective study that evaluated the supplementation of omega-3 fatty acids (800 mg/day for 12 months) in patients with endometriosis after conservative surgery, found that all women had an improvement of pelvic pain and dyspareunia compared to those receiving placebo.[70] In an observational cohort study the treatment with N-acetylcysteine (600 mg three times per day, 3 consecutive days per week) caused a slight reduction in diameter of endometriomas (-1.5 mm).[72] 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.[73] Statins, acting as competitive inhibitors of 3-hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, not only have intrinsic antioxidant activity but also perform antiproliferative and anti-angiogenic activity when administered at high doses.[74] In particular, simvastatin significantly reduced the proliferation of endometriotic stromal cells, inhibiting their adhesion to collagen fibers.[74] In 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.[75] Anti-inflammatory activity and modulation of ovarian steroid production by metformin led to investigate this drug in women with endometriosis. 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.[76] Treatment with tosiglitazone, ciglitazone or pioglitazone, which target a high affinity peroxisome proliferator-activated-γ (PPAR-γ), was able to inhibit proliferation and increased apoptosis of endometriotic cells. Several studies proved that they also caused regression of established experimental endometriotic implants in animals.[77] Among other anti-oxidants, retinoic acid decreased the number and the volume of endometriotic lesions with high vessel density in comparison with controls, after 17 days of therapy in mice.[78] Resveratrol, a natural antioxidant, exerts a potent anti-inflammatory effect by acting on several mechanisms such as NF-kB. In preclinical 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.[79] 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.[80] However these results were not confirmed by another trial in

which resveratrol (40 mg/day) was compared to a COC regimen (LNG 0.15 mg and EE 0.03 mg).[81] Epigallocatechin-3-gallate (EGCG) is one of the most abundant antioxidant polyphenols contained in green tea. Preclinical 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).[82]

Immunomodulators

TNF-α, an inflammatory cytokine, contributes to the proliferation of ectopic and eutopic endometrial cells, inducing multiple signaling pathways, such as the IKKβ complex, and NF-kB.[83] In baboons, two human recombinant TNF-α antagonists, TNFRSF1A and c5N, resulted in inhibitory activity on endometriotic lesions without affecting their menstrual cycle.[84, 85] Furthermore, etanercept, a fusion protein consisting of human recombinant soluble TNF receptor 2 conjugated to a human Fc antibody subunit, reduced the volume and histopathologic scores of rats' implants, decreasing serum levels of VEGF, IL-6 and TNF-α.[86] Infliximab, a monoclonal antibody directed against TNF-α, 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.[87] 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 been investigated *in vitro* and in animal models for the treatment of endometriosis. A reduction in the expression of genes that regulate the production of inflammatory cytokines, extracellular matrix metalloproteinases (MMPs), apoptosis inhibitors and VEGF was found, using these drugs.[88] Telmisartan, a combined blocker of angiotensin II type 1 receptor (AT1R) and activator of peroxisome proliferator-activated receptor (PPAR)-γ, was examined in murine model of endometriosis.[89, 90] In two preclinical 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. In particular, in both studies, telmisartan reduced the lesions' microvessel density and the number of Ki67-positive proliferating cells.[89, 90] 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.[91] 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.[92] 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%.[93] 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).

Epigenetic drugs

Epigenetic inhibitors are innovative investigational targets for treating endometriosis.[94] 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.[94] In a preclinical study, trichostatin A, a histone deacetylase, had antiproliferative 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, with a subsequent reduction of inflammatory cytokines production.[95] In another preclinical study, its administration in mice significantly decreased the size of endometriotic implants and improved the response to noxious thermal stimulus.[96] Valproic acid, another potent histone deacetylase inhibitor, was effective in decreasing the size of endometriotic implants of mice, being also well tolerated.[94]

Conclusions

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. Most currently available pharmacotherapies for endometriosis modulate symptoms by suppressing ovulation or inducing a hypoestrogenic state. Although some data demonstrate reductions in the size of endometriomas and colorectal lesions with medical treatment, medical therapies are used primarily for the management of pain and are unable to induce disease regression. There are no therapies that improve fertility outcomes in women with endometriosis, and nearly all hormonal medications inhibit ovulation. There are multiple goals for pharmacotherapy in patients with endometriosis, including the improvement of quality of life, pelvic pain, and disease burden. In addition, pharmacotherapy can be used to delay or decrease surgical interventions, improve postoperative pain control, and even achieve disease remission. Currently, a number of therapies are under study that address immunologic, angiogenic, and hormonal aspects of the disease pathogenesis. These treatments have the potential to better target the mechanisms that underlie the formation of endometriotic lesions to induce disease regression.

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