New trends in pharmacological treatments of endometriosis

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Abstract
Endometriosis is a chronic disease characterized by dysmenorrhea, dyspareunia, pelvic pain, and infertility. Endometriosis is often treated surgically upon diagnosis but with a high rate of recurrence, suggesting that a combination of surgical and medical management might provide better outcomes. The goal of medical treatment is to interrupt the growth and activity of endometriotic lesions, due to the chronic nature of this disease, long-term or repeated courses of medication may be required to control symptoms. Medical treatments since now recognize the use of gonadotropin-releasing hormone agonists, oral contraceptives, danazol and progestins. Increasing knowledge about the pathogenesis of endometriosis is providing the opportunity to use new agents for treatment, including antiinflammatory and antiangiogenesis compounds prevent or inhibit the development of endometriosis. The future perspective is to use a multiple approach for treating women with endometriosis with the goal of eradicate the disease and eliminate the symptoms.

Key words: endometriosis, medical treatment, progestins, oral contraceptive, aromatase inhibitors, omega-3, antiangiogenetic agents

Introduction
Endometriosis is a chronic condition characterized by growth of endometrial tissue in sites other than the uterine cavity. Common symptoms include dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. The etiology recognizes a number of theories on how endometrial tissue occurs outside the uterus, including retrograde menstruation through the fallopian tubes, transportation of tissue in the blood or lymph, and the local differentiation of mesothelial or blood cells into endometrium-like tissue [1]. The prevalence in women without symptoms is 2-50%, depending on the diagnostic criteria and the populations studied. The incidence is 40-60% in women with dysmenorrhea and 20-30% in women with subfertility [2]. The pathogenesis of the disease is multifactorial and includes an hormonal rearrangement (estrogen and progesterone) followed by ectopic implants proliferating and cytokines releasing that lead to inflammatory reaction that is associated with adhesions, fibrosis, scarring and anatomical distortion [3]. The problems of patients with endometriosis are disease-related symptoms and not implants per se, and treatments should be focused on resolution of complaints [4]. Current medical management of endometriosis is based on three major mechanism of action: iatrogenic menopause, pseudopregnancy and antinflammato-
associated with recurrent and deeply infiltrating endometriosis and has no systemic side effects and improved quality of life [6]. The use of vaginal danazol does not affect the menstrual cycle and has few side effects. The low-dose of danazol does not affect the pituitary ovarian axis and does not modify the endometrial thickness induced by estrogen and progesterone. The use of vaginal danzol administration seems to be a valid alternative to repeated surgery and in the treatment of infiltrating endometriosis pelvic pain and adenomiosis [7].

**Intra-uterine levonorgestrel releasing system**

An available levonorgestrel intra-uterine system (LNG-IUS) provides 20 μg/day of levonorgestrel locally in the pelvis, which results in atrophic endometrium and amenorrhea in up to 60% of patients without inhibiting ovulation. In recent studies of the LNG-IUS, slightly more than half of patients with chronic pelvic pain and mild to moderate endometriosis were satisfied or very satisfied with the treatment after 6 months [8]. The LNG-IUS may be an effective therapy for rectovaginal endometriosis, reducing dysmenorrhea and non-menstrual pelvic pain as well as significantly reducing deep dyspareunia and dyschezia [9].

**Oral progestins**

Desogestrel is demonstrated to be an effective, safe and low cost therapy of pain symptoms after endoscopic surgery for endometriosis. It shows a higher impact on breakthrough bleeding and a lower body weight increase respect to contraceptive pill [10].

Dienogest is a hybrid between progesterone and 19-nortestosterone derivates. It is an orally active, synthetic 19-nortestosterone derivate that exhibits selective binding to the progesterone receptors. Oral dienogest (2 mg/day for 12 weeks) was shown to be significantly better than placebo in reducing pelvic pain in patients with endometriosis in a double-blind trial, despite a substantial placebo response of approximately 21-26% for VAS (visual analogue scale) pain and improvement/satisfaction scores [11]. The improvements noted during treatment with oral dienogest (2 mg/day for 12-24 weeks) were sustained during long-term treatment for up to 65 weeks. In one study, the patients were shown to experienced continued improvement between 24 and 52 weeks after the treatment discontinuation [12]. Dienogest was not considered to be associated with significant androgenic effects and was generally well tolerated. The efficacy and tolerability of dienogest were sustained during long-term therapy for more than 1 year and remained effective for 6 months after treatment interruption [13].

**Estrogen-progestin combination**

A recent meta-analysis of 18 studies, suggest a protective effect of oral contraceptive (OCs) during use and a potential detrimental effect after discontinuation [14]. These results are somehow surprising and worrying, and they appear at odds with the well-recognized benefits of these agents for the treatment of endometriosis [15].

OCs treatment reduces the rate of post-operative endometrioma recurrence and should now be considered an essential part of long-term therapeutic strategies in order to limit further damage to future fertility [16]. Their effect is limited to the period of use, and endometriosis activity is reduced [17]. Continuous administration, without a 7-day break, to avoid withdrawal bleeding, may be more beneficial in terms of pain relief [18].

**New possible treatments**

**Aromatase inhibitors**

The use of aromatase inhibitors for medical management of endometriosis is still experimental and is based on the observation that endometriotic lesions express the enzyme aromatase and are able to make their own estrogen, even in the absence of gonadotropin stimulation [19]. Recent studies examined pain relief after 6 months of daily treatment with an aromatase inhibitor together with high-dose norethindrone acetate or an oral contraceptive and showed significant (but not complete) resolution of pelvic pain in women with endometriosis who had not responded to first-line treatment. Further research is required to determine if aromatase inhibitors will be safe and effective for long-term use in women with endometriosis pain [20]. Aromatase inhibitors are also believed to have the following roles in endometriosis-associated infertility: suppressing endometriotic lesions and ovarian stimulation agents [21].

**Antiangiogenic agents**

The emerging evidence that estrogens can both promote and inhibit endometrial vessel growth under different circumstances, demonstrates the complex regulation of endometrial angiogenesis. During the angiogenic process endothelial cells proliferate, migrate and attach to the external cellular matrix, inducing matrix remodeling, and formation of a new lumen in the endometrium of women with endometriosis [22].

Different antiangiogenetic treatments such as anti-VEGF agents and other angiostatic drugs have been
tested in experimental models of endometriosis with successful results inhibiting new vessels formation [23]. These drugs, mainly with cytotoxic properties, target specifically the endothelial cells without penetrate in the tissues.

Dopamine and dopamine agonists (bromocriptin, cabergoline) are able to promote the VEGFR-2 endocitosis in endothelial cells, blocking a critical step in the neoangiogenesis process and reducing the expression of VEGF in ectopic endometrium [24].

The thiazolidinediones (TZDs) are a class of medications used in the treatment of diabetes mellitus type 2, and have been shown to inhibit both monocyte migration and peritoneal inflammatory cells in a mouse model and modulate angiogenesis. A small trial currently exists in the literature in a limited series of patients with endometriosis treated with rosiglitazone for 6 months, suggesting the possibility of using TZDs for endometriosis pain relief in conjunction with attempts to conceive [25].

Antioxidants

Omega-3 polyunsaturated fatty acids have a role in the inflammatory process and a therapeutic effect has been suggested and two omega-3 fatty acids (DHA and EPA) significantly reduced the lipopolysaccharide induced IL-8, and PGE2, release decreasing the expression of Cox-2, underlying an inhibitory effect of omega-3 fatty acids on inflammatory mediators secretion, suggests a potential benefit in treatment of pelvic pain in patients with endometriosis [26]. Similar mechanism has been suggested to work for some therapeutic herbs [27].

Proapoptotic agents

Statins may be effective in the treatment of endometriosis, targeting growth and invasiveness of ectopic endometrial tissues as well as inflammation and oxidative stress associated with this condition. Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-co-enzyme A (HMG-CoA) reductase, a rate-limiting step of the mevalonate pathway, they decrease the mitogenic effect of IGF-I on endometrial stromal cells, moreover statins can interfere with angiogenesis (28). In addition statins possess anti-inflammatory, immune-modulatory properties, and anti-oxidant properties which may reduce the inflammatory reaction associated with endometriosis [29, 30].

Conclusions

The medical treatment of endometriosis in the next future will be enriched by several possible strategies. Hormonal and antiinflammatory drugs will be available in new formulations and their possible combination will be evaluated in order to defeat endometriosis.

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References


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