Best Practice & Research Clinical Obstetrics and Gynaecology xxx (2018) 1–10

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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From pathogenesis to clinical practice: Emerging medical treatments for endometriosis

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Keywords:
Endometriosis
Aromatase inhibitors
Antiangiogenic drugs
GnRH antagonist
Immunomodulators
Cannabinoids

A B S T R A C T

Endometriosis is a chronic disease, and a lifelong management plan should be developed by using pharmacological treatment and surgical procedures. The pathogenesis of endometriosis is complicated and has not been definitively established. The mechanisms involved are numerous, and their understanding is constantly evolving. Currently, the first-line drugs act by blocking ovarian function, creating an hypoestrogenic environment. The blockade of estrogen secretion and receptor activity and the activation of progesteron receptors are the main target of several current drugs, as well as those under development. The oral GnRH antogonists, the aromatase inhibitors, SERMs, and SPRMs are the hormonal drugs currently studied for treating endometriosis. The increasing knowledge of the pathogenesis has allowed the development of new treatments. The most studied are the anti-inflammatory drugs, starting from the new NSAIDs to the monoclonal antibodies and the statins. Among the antiangiogenic compounds, a role is suggested for Icon, PPARs, and HDACIs. A new class of drugs is the cannabinoids. The aim of this review was to investigate the new therapeutic hormonal and non-hormonal alternatives to standard treatments.

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https://doi.org/10.1016/j.bpobgyn.2018.01.021
1521-6934/© 2018 Published by Elsevier Ltd.

Please cite this article in press as: Clemenza S, et al., From pathogenesis to clinical practice: Emerging medical treatments for endometriosis, Best Practice & Research Clinical Obstetrics and Gynaecology (2018), https://doi.org/10.1016/j.bpobgyn.2018.01.021

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Introduction

Endometriosis is a chronic disease that requires a long-term management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures [1]. The pathogenesis of endometriosis has not been definitively established, but its increasing knowledge may permit to manipulate the signaling pathways involved and to develop new pharmacologic agents. The main basic pathogenetic events consist of an increased expression of estrogen receptors (ERs) and of a progesterone resistance in endometriotic tissue. Ectopic endometrial implants express the aromatase and 17β-hydroxysteroid dehydrogenase type 1 enzymes converting androstenedione into estrone and estrone into estradiol, respectively. Endometriotic cells have a reduced expression of 17β-hydroxysteroid dehydrogenase (17β-HSD) type 2 that inactivates estrogens. This combination allows the implants to be exposed to a high local concentration of bioavailable estrogens. On the contrary, the normal endometrium expresses high levels of dehydrogenase type 2 that guarantees an attenuated estrogen effect [2]. In addition to estrogen dependence, endometriosis is characterized by progesterone resistance owing to an overall reduction in progesterone receptors (PRs) and an absence of progesterone receptor-B compared to eutopic endometrium [3]. Progesterone normally triggers an endometrial response characterized by the inhibition of estrogen-dependent proliferation of epithelial cells, secretory maturation of the glands, and transformation of stromal cells into specialized decidual cells. Inflammation is another main pathogenetic factor, as the presence of ectopic tissue in the peritoneal cavity is associated with overproduction of prostaglandins, cytokines, and chemokines [4]. Other mechanisms such as cell proliferation and differentiation, apoptosis, migration, adhesion and invasion, neuroangiogenesis, aberrant endocrine signaling, and altered immunity seem to be involved [5]. Currently, first-line drugs act by blocking ovarian function, thereby creating a state of iatrogenic menopause or pseudopregnancy. The common medical treatments create an hypoestrogenic environment either by blocking ovarian estrogen secretion (GnRH-agonist, GnRH-a) or by inhibiting estrogenic stimulation of the ectopic endometrium (progestins and androgenic progestins) [6]. The present review shows the future innovative hormonal (GnRH antagonist, aromatase inhibitors (AIs), selective estrogen receptor modulators, and selective progesterone receptor modulators) and non-hormonal treatments (nonsteroidal anti-inflammatory drugs [NSAIDs], immunomodulators, anti-angiogenic agents, and cannabinoids) of endometriosis.

Hormonal treatments

GnRH antagonists

Gonadotropin-releasing hormone (GnRH) antagonists suppress pituitary gonadotropin hormone production and create a dose-dependent hypoestrogenic state to inhibit endometriotic cell proliferation. Novel GnRH antagonists proposed for endometriosis treatment are the oral nonpeptide forms (Elagolix, Abarelix, Ozarelix, and TAK-385) [7]. Elagolix, a short-acting, nonpeptide, GnRH antagonist is a promising drug for endometriosis with positive results from clinical trials [8]. Compared to the classic GnRH antagonists, it has the advantage of being administered orally. It causes a dose-dependent suppression of LH, FSH, and E2, while progesterone concentrations remained at unovulatory levels. Two similar, multicenter, double-blind, randomized, 6-month, phase III trials (Elaris Endometriosis I and II, EM-I and EM-II) [9] compared two different doses of elagolix (150 mg once daily or 200 mg twice daily) with placebo. In both trials at 3 months, a significant reduction in dysmenorrhea was reported (about 44%, 74%, and 21% for low-dose, high-dose, and placebo groups, respectively) along with nonmenstrual pelvic pain (about 50%, 56% and 36% for low-dose, high-dose, and placebo groups, respectively) and consequently an improvement in quality of life. Although more than 72% of women have reported adverse events (hot flashes, headaches, nausea, and insomnia), in most cases, they were mild or moderate. The treatment groups also reported a decrease in bone mineral density and an increase in serum lipid levels caused by the hypoestrogenic effect of drugs. Further studies are necessary to compare elagolix to current medication, to evaluate the necessity of estrogen-progestin add-back therapy supplementation to reduce loss of bone mineral density, and to indagate the drug effects on ovarian function, in particular ovulation, as several pregnancies were described during intake of elagolix [10].

Please cite this article in press as: Clemenza S, et al., From pathogenesis to clinical practice: Emerging medical treatments for endometriosis, Best Practice & Research Clinical Obstetrics and Gynaecology (2018), https://doi.org/10.1016/j.bpobgyn.2018.01.021

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