Biomedicine & Pharmacotherapy 90 (2017) 575–585

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

A peek into the drug development scenario of endometriosis – A systematic review

Luxitaa Goenka[a], Melvin George[a,*], Maitrayee Sen[b]

[a] Dept of Clinical Pharmacology, SRM MCH & RC, Kattankulathur, Chennai, Tamil Nadu, 603203, India
[b] Dept of Obstetrics & Gynaecology, SRM MCH & RC, Kattankulathur, Chennai, Tamil Nadu, 603203, India

ARTICLE INFO

Article history:
Received 27 December 2016
Received in revised form 18 March 2017
Accepted 27 March 2017

Keywords:
Endometriosis
New drugs
Drug development
Elagolix
Clinical trials

ABSTRACT

Purpose and objective: Endometriosis is a gynaecological disease that is characterised by the presence of endometrium like tissue-epithelium and stroma that develops outside the uterine cavity, which is responsible for pelvic pain and infertility. Even though several medical therapies exist for the treatment of endometriosis, each of the drug class has its own limitations such as cost of treatment, side-effects and its short-term effect on the symptoms of endometriosis. In this review, we have attempted to summarize the current status and challenges of drug development for endometriosis.
Methods: A systematic review was done and all the RCTs were selected from the identified hits. We included studies that explored the usage of therapeutic drugs on endometriosis patients from inception till November 2016. The search term used was 'Endometriosis' using PubMed and Clinicaltrials.gov. For the final analysis, 60 articles were analyzed and we identified the newly emerging drug therapies for endometriosis treatment and have briefed their current status and challenges in drug development for endometriosis. The quality of the selected studies was assessed based on the degree of bias.
Results: The current classes of drugs that have shown promising therapeutic results include Gonadotropin- releasing hormone (GnRH) antagonists, aromatase inhibitors (AI), and selective progesterone and estrogen receptor modulators, dopamine receptor-2-agonists and statins. The drugs that failed midway during development include tanezumab, rosiglitazone, infliximab, pentoxifylline, telapristone acetate, asoprisnil and raloxifene.
Conclusion: From the literature review, it appears that the most promising molecules for the treatment of endometriosis in the near future include elagolix, mifepristone, TAK-385, KLH-2109 and ASP1707 and cabergoline. It remains to be seen if these molecules would succeed large phase 3 clinical trials and overcome the regulatory hurdles to become an essential tool in the gynaecologist's armamentarium against endometriosis.

Contents

* Corresponding author.
E-mail address: melvingeorge2003@gmail.com (M. George).

http://dx.doi.org/10.1016/j.biopha.2017.03.092
0753-3322/

1. Introduction

Endometriosis is a chronic gynaecological disease that is characterised by the presence of endometrium like tissue-epithelium and stroma that develops outside the uterine cavity, which is responsible for pelvic pain and infertility. The endometric lesions is primarily present on the ovaries, bowel and tissue lining the pelvis, howbeit it may also exist in the pericardium, pleura, lung parenchyma and brain. Endometriosis is a disease that has a destructive effect on the quality of life (QOL), social, occupational and psychological functioning [1]. The incidence of endometriosis in women aged between 15 and 50 years is 0.14–3.5% [2–4]. The risk factors of endometriosis include early menarche, short menstrual cycles, late menopause, low body mass index (BMI), nulliparity, increased consumption of alcohol, caffeine and prolonged menstruation [5–8]. Endometriosis is an extremely variable condition in its presentation, symptomatology and likelihood of recurrence. The effective management requires an individualised approach [9]. The current therapeutic strategies for endometriosis include surgical and pharmacological therapies; the pharmacological therapies are classified into hormonal and non-hormonal treatments. The objectives of medical management include relief of pain, prevention of recurrence and enhancing fertility in women who desire to have children. In spite of several therapeutic modalities existing for these patients, the disease is notorious for its recurrence and till date there is no curative medication available for the ailment [10,11]. The first line treatment for endometriosis includes oral contraceptive pills and progestogens which are associated with significant limitations (Table 1). Thus, it is essential to develop effective and well-tolerated medical therapies that would be pertinent for the long-term treatment of endometriosis. It has been clearly recommended by Royal College of Obstetricians and Gynaecologists (RCOG) that suppression of ovarian function to improve fertility in minimal to mild endometriosis is not effective and should not be offered for this indication alone. There is no evidence of its effectiveness in severe disease. Therefore, overall there is no evidence to support the use of ovarian suppression agents in the treatment of endometriosis-associated infertility. More harm than good may result from the treatment, because of adverse effects like the lost opportunity to conceive.

The drugs that are being explored as potential therapeutic options for endometriosis include hormonal agents such as Gonadotropin-releasing hormone (GnRH) antagonists, aromatase inhibitors (AI), and selective progesterone and estrogen receptor modulators that seek to modify the hormonal milieu of the disease and non hormonal agents such as anti-angiogenics, TNF-α blockers, anti-nerve growth factor inhibitor antibody, statins, peroxisome proliferator-activated receptor gamma ligands (PPARs) that targets diverse mechanisms such as angiogenesis, inflammation and immune-deregulation. In this review, we have attempted to summarize the current status and challenges of drug development for novel upcoming pharmacological molecules for the treatment of endometriosis by performing a systematic review of the literature.

2. Methodology

2.1. Protocol and registration

We did not register the protocol of our systematic review in any registry.

Table 1
Limitations of current drug therapy for treatment of endometriosis .

Drug type	Examples of Drugs	Limitations
Combination estrogen/progestin Contraceptives/ progestogens [35,73,76,77]	Norethindrone acetate Ethinyl estradiol Gestodene Dienogest Medroxyprogesterone (DMPA)	Due to its effect on ovulation the treatment may be limited to women who do not wish to conceive. Androgenic side-effects (hair growth, mood changes, liver damage, arterial thrombosis). Other adverse effects include weight gain, nausea, breast tenderness, mastalgia, hot flushes, decreased libido and vaginal dryness.
GnRH agonist [77–80]	Goserelin (Zoladex) Leuprolide (Lupron Depot, Eligard) Nafarelin (Synarel) Buserelin	Even though endometric atrophy is achieved by GnRH agonist the, endometric cells express an aromatase enzyme that ensures its survival that is independent of ovarian steroids. Other adverse events include hypoestrogenic effects (Hot flushes, Vaginal dryness, Decreased libido, Genital bleeding)

DMPA, Depot medroxyprogesterone acetate; GnRH, Gonadotropin-releasing hormone.