Emerging treatment of endometriosis

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Abstract  Current treatment of endometriosis is mainly based on surgery and ovarian suppressive agents (oral contraceptives, progestins, GnRH agonist and androgenic agents). Hormonal treatments are often associated with unwanted effects, delayed conception and recurrence of disease and symptoms when stopped. For these reasons, new drugs that aim new targets are required to cause regression of the disease & symptoms without adverse hypo-estrogenic effects. This review aims to provide an update on the new drugs used for treatment of endometriosis. These include the levonorgestrel-releasing intrauterine device, GnRH antagonists, aromatase inhibitors, selective estrogen-receptor modulators, progesterone antagonist, selective progesterone receptor modulators, angiogenesis inhibitors, and immunomodulatory drugs.

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1. Introduction

Endometriosis is a common estrogen-dependent disorder that can result in substantial morbidity, including pelvic pain, multiple operations, and infertility. Current treatment of endometriosis is mainly based on surgery and ovarian suppressive agents. Approximately only half of women with endometriosis get pain relief from existing medical or surgical treatments. Currently available medical therapies are designed to suppress estrogen synthesis, inducing atrophy of ectopic endometriotic implants or interrupting the cycle of stimulation and bleeding. Oral contraceptive, androgenic agents, progesterins and gonadotropin-releasing hormone analogues have all been successfully used in the treatment of endometriosis. Unfortunately, these hormonal treatments are often associated with unwanted effects caused by a hypo-estrogenic state. Furthermore, recurrence of disease and symptoms is quite common with all available drugs. An ideal treatment for endometriosis would induce regression of the disease and its symptoms without any adverse effects associated with a hypo-estrogenic state. None of these drugs can eradicate the disease and, in some cases, the substantial side effects limit the long-term use of these therapies. Current medical therapies for endometriosis result in delayed conception and have not been shown to provide any fertile benefit subsequent to treatment. For these reasons, new drugs that aim new targets are under development (1). These include the levonorgestrel-releasing intrauterine device, GnRH antagonists, aromatase inhibitors, selective estrogen-receptor modulators, progesterone antagonist, selective progesterone receptor modulators, angiogenesis inhibitors, and immunomodulatory drugs.

2. Levonorgestrel-releasing intrauterine device (LNG-IUD)

Although oral progestogens for treatment of endometriosis are effective and cheap, their efficacy is significantly influenced by poor compliance and systemic side effects (2). LNG is a potent steroid widely used in oral contraceptives and subdermally implanted contraceptive devices. It is a T-shaped intrauterine system, developed as a contraceptive device which releases LNG in the uterine cavity. The release rate of LNG from the intrauterine releasing system is 20 μg per 24 h during the first year, and it slowly decreases throughout the 5 years of use. The released progestogen induces endometrial atrophy although ovulation is usually not suppressed. This results in hypomenorrhea or amenorrhea and reduced dysmenorrhea (3).

An increasing number of publications indicate an emerging role for the LNG-IUD in the treatment of endometriosis. In patients with surgically proven peritoneal as well as rectovaginal endometriosis, the first pilot studies showed a great improvement in pain control as well as a reduction in ultrasonographic dimensions of the rectovaginal nodules (3,4).

A significant reduction of pain as well as staging of the disease observed in 34 women with laparoscopically confirmed minimal to moderate endometriosis over a period of 6 months (5). The LNG-IUD is an effective hormonal option for treating symptomatic endometriosis (minimal to moderate). With a continuation rate of 68% after 6 months, it has the potential for providing long-term therapy in a substantial number of sufferers. The presence of adhesions was, as expected, not altered.

Two randomized trials (6,7) were published on LNG-IUD use in endometriosis. The first (6) study compared expectant management with immediate treatment with the LNG-IUD after laparoscopic surgery for symptomatic endometriosis in 40 women. Twelve months after surgery dysmenorrhea scores were significantly lower in the LNG-IUD group compared with the expectant management group. The second trial (7) compared the efficacy of an LNG-IUD and a GnRH-agonist analog in the control of chronic pelvic pain in 83 women with stage I–IV endometriosis during a period of 6 months. Both, the LNG-IUS and the GnRH-analogue were effective in the treatment of chronic pelvic pain-associated endometriosis, although no differences were observed between the two treatments.

Although the exact mechanism of action of the LNG-IUD is unclear, recent evidence (8) shows that the LNGIUD delivers significant amounts of LNG into the peritoneal fluid, clearing up the local effect on the endometriotic implants which may be mediated through estrogen and progesterone receptors, most probably inducing decidualization. As peritoneal fluid levels of LNG were closely related to the levels in serum, this suggests a dominant hematogenic mechanism by which LNG reaches the peritoneal cavity.

A Cochrane systematic review evaluated postoperative use of an LNG-IUD in women with endometriosis (9). Limited evidence from one small study has shown that postoperative use of the LNG-IUD reduces the recurrence of painful periods in women who have had surgery for endometriosis. There is a need for further, well-designed RCTs of this approach.

In conclusion, for women with endometriosis who need long-term treatment, the LNG-IUD may be a treatment of choice since it permits the same system to be used for at least 5 years with no modifications in estrogen levels and few hypoestrogenic side effects (7). In the long term it is a low-cost therapy with usually fewer side effects than other progestogenic
agents. Among the additional advantages of the LNG-IUS is the fact it requires only one medical intervention for its introduction every 3 years. This device could therefore become the treatment of choice for CPP-associated endometriosis in women who do not wish to conceive. Further studies are required before this device can be recommended as a treatment for endometriosis-associated pelvic pain.

3. GnRH antagonists

Gonadotropin releasing hormone agonist analogues have one serious problem; when first administered, they cause an increase in LH and FSH secretion and an increase in estradiol production. For women with pelvic pain, the increase in ovarian estrogen production is associated with increased pelvic pain and decreased quality of life (10). However, the agonist phase is typically limited to the first 5–10 days of treatment. Recently, GnRH antagonists that immediately block GnRH effects have been developed for clinical use in endometriosis, leiomyoma, breast cancer, premenstrual syndrome, polycystic ovary syndrome, and ovulation induction for in vitro fertilization (IVF) (11).

The main mechanism of action of the GnRH antagonists is competitive receptor occupancy, which results in the blockade of GnRH receptor dimerization, a biochemical process that is required for receptor activation. The antagonistic properties of GnRH exert their effect by competing with endogenous GnRH for pituitary binding sites (12). The GnRH antagonists suppress LH secretion in a dose-dependent manner. At small doses, the suppression of LH is minimal. At large doses, near-complete suppression of LH can be achieved.

In one preliminary study, a total of fifteen women received 3 mg of cetrorelix (Cetrotide) weekly for eight weeks (13). Circulating estradiol was suppressed to a mean of 50 pg/ml. All patients reported a symptom-free period during GnRH antagonist treatment. Regression occurred in more than half of the cases and the degree of endometriosis declined to a mild stage on second look laparoscopy.

Another GnRH antagonist, abarelix, has been demonstrated to be effective in the treatment of pelvic pain caused by endometriosis (14). However, side effects may have slowed the progress of the development of this antagonist for treatment of endometriosis.

In conclusion, GnRH antagonists seem to be useful in the treatment of endometriosis in most cases. Furthermore, fewer side effects, such as postmenopausal symptoms, occur with this agent and no estradiol add-back is needed. The GnRH antagonist analogues may be superior to GnRH agonists because they produce immediate suppression of LH and FSH secretion and avoid the agonist phase of GnRH agonist therapy. In the future, nonpeptidic GnRH antagonists are expected to be available for oral administration. Although they are still under investigation, these agents have the potential to improve patients’ comfort and compliance (15).

4. Aromatase inhibitors (AIs)

4.1. Aromatase activity

Medical treatments usually are directed at inhibiting estrogen action or its production from the ovaries and do not address local estrogen biosynthesis by the aromatase enzyme in endometriotic lesions. Aromatase activity is expressed in several types of cells in the reproductive system including the ovarian granulosa cell, the placental syncytiotrophoblasts and the testicular Leydig cells (16). Aromatase is the key enzyme in estrogen biosynthesis. It catalyzes the conversion of C19 steroids to estrogens (estrone and estradiol). Therefore, there are no important downstream enzymes to be affected, with the result that aromatase is an excellent target for inhibition of estradiol synthesis. In addition, because estrogen is needed to stimulate ectopic endometriotic tissues in patients with endometriosis and because of the in situ presence of aromatase in these tissues, blockage of aromatase activity in these endometriotic sites with an AI is a rational approach to medical treatment of endometriosis (17).

In women with endometriosis, it has been shown that there is an increased expression of cytochrome P450 aromatase in endometrial tissue, but not in women without endometriosis (18). Although the normal endometrium contains no detectable levels of aromatase activity, this enzyme is induced to very high levels in endometriotic tissue by the inflammatory mediator prostaglandin estradiol (E2) to increase local estrogen production in the disease implants.

4.2. Aromatase inhibitors

The AIs are classified into type I and type II inhibitors. Both types of inhibitors compete for binding to the active site. Enzyme activity is then permanently blocked due to an unbreakable bond between the inhibitor and enzyme protein (19). Several potent and selective third-generation AIs are available; of these, anastrozole and letrozole have substantial advantages over earlier agents in terms of efficacy and tolerability. AIs are FDA approved to treat postmenopausal women with estrogen receptor positive breast cancer refractory to tamoxifen. Although these agents have been widely used to treat postmenopausal or anovulatory patients with breast cancer, clinical experience with AIs in women with endometriosis is still limited (20). AIs act by blocking aromatase, which converts androstenedione to estrone, an estrogen derivative (21). Its mechanism of action is by decreasing local production of estrone causing a low estrogen milieu. Decreasing aromatase in the brain specifically is thought to decrease LH and FSH, which, in turn, leads to a decrease in estrogen levels as well.

Because the initial response to the effects of AIs is a decrease in estrogen levels, there is an increase in FSH and LH. This increase in FSH and LH directly stimulates the ovary. Stimulating the ovary leads to an increased number of mature follicles (22). Therefore, using an AI can treat pain associated with endometriosis, but can also treat the infertility aspect when used for ovulation induction and in IVF protocols. The two AIs mainly used for endometriosis pain and infertility are anastrozole and letrozole, both third generation drugs.

4.3. Uses in postmenopause

In the first published report of the use of an AI (anastrozole) for the treatment of endometriosis, a 57 year old woman with severe recurrent endometriosis experienced complete relief of pain after 2 months of treatment. (23). Recently Mousa et al.
observed. The size of ovarian endometriomas was reduced.

6 months. Disappearance of ovarian endometrioma and reduc-

sion in pelvic pain in all cases at the end of 6 months were

tablet of 0.15 mg of desogestrel, and 0.03 mg of ethinyl estra-

sis hormone therapies, women took letrozole (2.5 mg), one

patients who refuse surgery and fail to respond to other

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AIs improve pain and urinary symptoms in patients with blad-

and the patient underwent laparoscopic partial cystectomy.

ly improved pain and urinary symptoms in both patients. One

in both cases. Pregnancy was achieved in both cases after two

years. Side effects were minimal and well tolerated by both

with the combination of an AI, a progestin, and serial cyst

rent abdominal wall endometrioma was managed successfully

with the combination of an AI, a progestin, and serial cyst

aspiration (25).

4.4. Uses in premenopause

In premenopausal women, an AI alone may induce ovarian

folliculogenesis, and thus AIs are combined with a progestin,

a combination oral contraceptive, or a GnRH analogue in

order to prevent reflex increments in luteinizing hormone

and follicle stimulating hormone. A small pilot study of 10

reproductive aged women demonstrated that a combination

of letrozole (2.5 mg/day), norethindrone acetate (2.5 mg/day),

calcium and vitamin D for 6 months is effective in both reduc-

ing laparoscopically visible endometriotic lesions and decreas-

ing pelvic pain scores (26). In another study, two

premenopausal sisters (24 and 26 years old) were diagnosed

with endometriosis by laparoscopy and failed to respond to

conventional treatment including oral contraceptives and

GnRH analogues. An AI (anastrozole 1 mg/day) was given

with progesterin (200 mg/day) for 6 months. The treatment

resulted in a rapid progressive reduction in symptoms with

the maintenance of remission of symptoms and absence of

endometriotic lesions for more than two years after treatment

in both cases. Pregnancy was achieved in both cases after two

years. Side effects were minimal and well tolerated by both

patients (27). Two premenopausal patients with bladder

endometriosis were treated with letrozole (2.5 mg/day),
norethisterone acetate (2.5 mg/day), elemental calcium and

vitamin D3 for 6 months (28). The double-drug regimen quick-

ly improved pain and urinary symptoms in both patients. One

patient had no significant adverse effect and continued the

therapy for 14 months. The other patient developed myalgia

and severe arthralgia; pain and urinary symptoms recurred

few months after the interruption of the 6-month treatment

and the patient underwent laparoscopic partial cystectomy.

AIs improve pain and urinary symptoms in patients with blad-

der endometriosis; however, severe side effects of treatment

may occur. These agents should be administered only to

patients who refuse surgery and fail to respond to other

therapies.

In a non-randomized initial study, Amsterdam et al.
evaluated 18 reproductive aged women with refractory pain
from endometriosis who failed two other therapies (29). They
were administered anastrozole 1 mg for 6 months in addition
to a continuous oral contraceptive pill to prevent pregnancy.
This study found there was a decrease in pain scores associated
with the combination of anastrozole and OCP.

Very recently, Letrozole given with combined pills achieved
complete regression of recurrent endometriotic cysts and pain
relief in all cases (30). After a 6-month washout of endometrio-
sis hormone therapies, women took letrozole (2.5 mg), one
tablet of 0.15 mg of desogestrel, and 0.03 mg of ethinyl estra-
diol, calcium (1200 mg), and vitamin D3 (800 IU) daily for
6 months. Disappearance of ovarian endometrioma and reduc-
tion in pelvic pain in all cases at the end of 6 months were
observed. The size of ovarian endometriomas was reduced
after 3 months. Pain scores decreased only after 1 month of

treatment and continued decreasing in each treatment month.
Overall, no significant change in bone density was detected.

A prospective, randomized trial showed that 6 months of

treatment with anastrozole (1 mg/day) and goserelin compared

with goserelin alone increased the pain-free interval and

decreased symptom recurrence rates in patients after surgery

for severe endometriosis (31).

4.5. Side effects

Side effects of AIs are rare, but include headaches and diar-
rhea. Because AIs decrease estrogen in local tissues, it can
increase the risk of osteoporosis (32). One study found no
change in bone density at 6 months after use of an AI with
an oral contraceptive in premenopausal women, and another
found a decrease in bone density with the use of AI with a
GnRH agonist after 6 months of use in premenopausal women
(33). One case report demonstrated that exemestane was used
to successfully treat pain in refractory endometriosis and might
be a better choice than other AIs because it is potentially bone
sparing (24). Larger, randomized, controlled studies will need
to be done to evaluate the effect of AIs on bone density of
reproductive aged women. It is likely that if a true decrease
in bone density is found, there will be time limitations such
as with depo-provera, as well as recommendations to supple-
ment calcium in these patients. Letrozole is the most common
AI used for ovulation induction. It is given cyclically for infer-
tility compared with continuously if used for pain (22). Letro-
zele is not FDA approved for this indication and there is a
black box warning regarding using this medication in pregnant
women. One study found that in 911 births that were con-
ceived by using either clomiphene citrate (CC) or letrozole
for ovulation induction, the rate of both chromosomal anomali-
ies as well as major congenital malformations was the same in
the CC and letrozole group (34).

In conclusion, all three combinations were shown to
decrease pain in patients with refractory endometriosis. Regi-
mens which include combinations of an AI with a progestin
or oral contraceptive will probably become more popular than
combinations of an AI with a GnRH analogue because the for-
mer are cheaper with fewer side effects, and may be adminis-
tered long term or for repeated courses (21). Limited data
are available on the long-term course of pain symptoms after
completion of treatment with AIs; however, some recent stud-
ies suggest that symptoms may recur at short-term follow-up
(35). No severe adverse effect has been reported during treat-
ment with AIs both in pre- and postmenopausal women. On
the basis of the available data, administration of AIs should
now be offered only to the small number of women who have
severe pain despite previous surgical and hormonal therapies.
Further research in the form of larger sample size randomized
controlled trials will be required before recommending the rou-
tine use of these agents.

5. Selective estrogen receptor modulators (SERMs)

Non-steroidal anti-estrogens that bind to estrogen receptors
(ERs) and can act as either estrogen agonists or antagonists,
depending on the target tissue, are known as SERMs (36).
They can be targets toward the α- or β-subunits of the estrogen
receptor. Raloxifene is a second-generation SERM that has been shown to prevent osteoporotic fractures and holds promise for the prevention of breast cancer. In contrast to tamoxifen, a first-generation SERM, raloxifene has an antiestrogenic effect on endometrial tissue. SERMs are best known for their use in menopause and breast cancer.

There is emerging data indicating that this class of medication, specifically agonists toward the β-subunit, may be able to be used to treat endometriosis. The β-subunit is felt to act on different targets than classic α-SERMs, such as bone, mammary and endometrium (37). SERMs directed toward the β-subunit have been found to have anti-inflammatory action in several rat models toward other inflammatory mediated diseases, such as inflammatory bowel disease and rheumatoid arthritis (38). One study demonstrated that SERMS resolved endometriosis in 40–75% of mice treated with a SERM directed toward the β-subunit (37). Its effects in human clinical studies are not yet known.

6. Progesterone antagonist

Mifepristone (RU-486) is best known for its use in medical abortions (39). Mifepristone is an oral active progesterone antagonist at the receptor level. It also has a high affinity for progesterone and glucocorticoid II receptors. With its antiprogestosterone effect, mifepristone prevents progesterone from exerting its action. It also has a direct inhibitory effect on human endometrial cells and it can modulate the estrogen and progesterone receptor expression in both eutopic and ectopic endometrium.

Both mifepristone and onapristone another drug with progesterone antagonist properties have been shown to have promising effects on endometriosis in the rodent model (40,41). Several non-randomized small trials have demonstrated a reduction of pain, as well as decrease in visible disease at time of laparoscopy (42,43). These trials have all used ≤100 mg. Kettel et al. published a series of studies of administration of different doses of mifepristone in women with endometriosis. A minimum dose of 50 mg mifepristone for six months demonstrated a significant regression in visible endometriotic lesions and a decrease in clinical symptoms. On the other hand, treatment of endometriosis patients with mifepristone 5 mg per day in an uncontrolled pilot study resulted in pain improvement but no change in endometriotic lesions, suggesting this dosage is too low to achieve acceptable efficacy (42). Side effects are usually seen with doses of ≥200 mg. These side effects are due to the antagonistic affinity of the drug to glucocorticoid receptors causing a hypothalamic state.

Further large randomized clinical trials on the use of mifepristone in women with endometriosis should be performed in the future.

7. Selective progesterone receptor modulators (SPRM)

SPRM are novel progesterone receptor ligands with a high degree of endometrial selectivity that exhibit agonist/antagonist effects based on the target tissue, dose and presence or absence of progesterone (44). They have the potential to induce reversible amenorrhea through selective inhibition of endometrial proliferation, a direct effect on endometrial blood vessels and the potential to suppress endometrial prostaglandin production in a tissue-specific manner without the systemic effects of estrogen deprivation, providing a rationale for the treatment of endometriosis-related pain (45).

Asoprisnil is the first SPRM to reach an advanced stage of clinical development for the treatment of endometriosis. Asoprisnil can suppress both the menstrual cycle and endometrial growth (46). To date, there is only one published randomized, placebo-controlled trial (47) of asoprisnil (5, 10 and 25 mg/day) for 12 weeks in 130 women with a laparoscopic diagnosis of endometriosis who exhibited moderate or severe pelvic pain at baseline. All doses of asoprisnil reduced non-menstrual pelvic pain similarly as well as dysmenorrhea; however, the effect on bleeding pattern was dose-dependent. A separate study with an identical design using different asoprisnil doses showed that 5 mg is the minimum effective dose for pain relief in subjects with endometriosis (48).

SPRM have many potential benefits over other therapies. First, they can disrupt cycling in patients without the low-estrogen milieu that causes many side effects in GnRH agonists. In relationship with antiprogesterones, they are more specific for the progesterone receptors thus not inhibiting the glucocorticoid receptors as well (49). No serious, drug-related adverse events were reported during the treatment or follow-up period. A favorable safety and tolerability profile of asoprisnil with no signs of estrogen deprivation was reported.

8. Angiogenesis inhibitors

Retrograde menstruation with peritoneal attachment is believed to lead to the development of endometriotic lesions. However, this shed endometrial tissue requires the establishment of a new blood supply in order to survive in the peritoneal cavity (50). The endometrium has angiogenic potential, and endometriotic lesions grow in areas with a rich vascularization, suggesting that angiogenesis is a prerequisite for endometriosis development. Therefore, inhibition of proangiogenic factors (e.g. VEGF and MMPs) may offer new therapeutic opportunities (51). Anti-vascular endothelial growth factor agents and other antiangiogenic drugs (i.e., TNP470, endostatin, anginex, rapamycin) have been studied in laboratory and animal models for treatment of endometriosis. The effectiveness of angiostatic compounds in reducing the growth of endometriotic lesions has been shown in the mouse model (52). Only one human study (53) has been performed thus far suggesting that the angiostatic (and immunomodulatory) compound thalidomide may be effective in women with relapsing endometriosis.

A novel, non-hormonal, approach to treat endometriosis may be found in the use of statins. Statin originally developed to treat heart disease and prolong life expectancy, and statins lower blood cholesterol levels by inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, an enzyme that controls the rate of cholesterol production (51). There are potentially very exciting other benefits, such as reducing the risks of diabetes, dementia and even osteoporosis. A recent report (54) demonstrated that statins also inhibit the growth of human endometrial stromal cells in vitro, which opens a promising new field in endometriosis research.

Rapamycin is a widely used drug with antifungal, immunosuppressant and antiangiogenic effects. A recent animal study
demonstrated that administration of rapamycin significantly reduced the size of the endometriotic lesions (55). This was associated by inhibition of VEGF-mediated angiogenesis as indicated by a suppression of endothelial cell sprouting in vitro and a reduction of microvessel density in endometriotic lesions in vivo. Rapamycin induces regression of endometriotic lesions by inhibiting neovascularization and cell proliferation.

Dopamine and its agonists, such as cabergoline (Cb2), promote VEGF receptor-2 (VEGFR-2) endocytosis in endothelial cells, preventing VEGF/VEGFR-2 binding and reducing neoangiogenesis (50). Recent study evaluated the anti-angiogenic properties of Cb2 on growth of established endometriosis lesions. A significant decrease in the percentage of active endometriotic lesions and cellular proliferation index was found with Cb2 treatment. Neoangiogenesis was reduced by Cb2 treatment, as observed at gross morphological level and by significant changes in gene expression. Cb2 treatment in experimental endometriosis has an anti-angiogenic effect acting through VEGFR-2 activation. These findings support the testing of dopamine agonists as a novel therapeutic approach to peritoneal endometriosis in humans.

Recently, the effect of dopamine agonist quinagolide on endometriotic lesions in patients with endometriosis-associated hyperprolactinemia was evaluated (56). Quinagolide induced a 69.5% reduction in the size of the lesions, with 35% vanishing completely. By interfering with angiogenesis, enhancing fibrolysis, and reducing inflammation, quinagolide reduces or eliminates peritoneal endometriotic lesions in women with endometriosis.

The potential, limitations and challenges of antiangiogenic therapy for the treatment of endometriosis have been explored (57). Antiangiogenic agents tested so far have proven effective for preventing neo-vascularization of endometriotic lesions and are likely to be efficient for early-stage disease. However, antiangiogenic treatments may alter reproductive function by impairing physiological angiogenesis, the greatest concern being the potential risk of teratogenicity. The initial promise of vascular therapy has not yet been fulfilled, mainly due to the limited selectivity of the vascular therapies available. The ongoing evolution in genomics and proteomics is revolutionizing the discovery of novel, disease specific endothelial markers, leading to improved ligand-based treatments. Combining angiostatic agents and VDAs with medical and surgical therapies in an adjuvant setting, e.g. with a view to preventing relapse or improving drug efficacy, may serve to accelerate the introduction of vascular drugs in the context of endometriosis treatment. This would probably be the quickest and most efficient way of enhancing current treatment modalities.

In conclusion, the vasculature is a promising target because of its genetic stability, easy access via the circulation and amplifying action during treatment. The administration of antiangiogenic drugs has been proved to reduce the establishment, maintenance and progression of endometriotic lesions in different laboratory and animal models; however, further investigations are required before clinical trials can be planned in humans. The role of antiangiogenic compounds in the treatment of endometriosis remains to be defined. It appears unlikely that antiangiogenic drugs may cure the symptoms caused by large endometriotic nodules that are mainly composed by fibromuscular tissue (58); on the contrary, these agents may have a role in the postoperative treatment of endometriosis to increase the pain free interval and decrease the recurrence of the disease.

9. Immunomodulators

The mounting evidence shows that altered immune function plays a crucial role in the genesis and development of endometriosis. It has become clear that pelvic inflammation, increased macrophage activation and invasion of the extracellular matrix are potential targets for endometriosis treatment and/or prevention (51). Immunomodulators are thought to work by decreasing the inflammatory response to disease. The molecules that allow for ectopic endometrial cells to implant on the peritoneum and begin growing are thought to be mediated through this process (1). Most of these compounds have not been thoroughly tested in humans, but initial studies in rodent models are promising. This broad group of medications includes loxoribine, IFN-α2 β and TNF-α inhibitors.

Lxoribine is thought to stimulate natural killer cells, which then do not allow endometrial cells to implant in ectopic tissues. One small study in rat models showed that there was a significant reduction in amount of disease (39).

IFN-α 2 β is another immunomodulator that has been shown to decrease endometriosis in animal models and in tissue cultures (1). The route of administration of this medication is by intraperitoneal placement during laparoscopy or by subcutaneous injections. Due to this invasive administration, this drug would likely be approved only for refractory disease. One small, prospective randomized study found that intraperitoneal treatment with IFN-α 2 β during surgery with a GnRH agonist postoperatively increased recurrence risk after surgery (60).

One of the most promising interventions seems to be the selective blocking of TNF-α production. Therapeutic manipulation of the immune system through TNF-α inhibitors may be beneficial in women with endometriosis (61). TNF-α inhibitors, such as etanercept, are a new form of therapy mostly used for rheumatoid and autoimmune diseases. They work by decreasing production or release of TNF-α from macrophages. TNF-α inhibitors may have role in preventing disease progression or causing regression of early stage disease. In the rodent (61) and baboon model (62), it has been shown that TNF-α binding protein is able to inhibit the development of endometriosis and endometriosis-related adhesions. In humans, however, the evidence is not so promising. There is one case report of patient with advanced endometriosis who was on a TNF-α inhibitor and who showed no improvement of infertility or endometriosis based on laparoscopy after several years of taking the medication (63). A randomized placebo-controlled trial was designed with 21 women with severe pain and a rectovaginal nodule (64). After 1 month of observation, three infusions of an anti-TNF-alpha monoclonal antibody (infliximab; 5 mg/kg) or placebo were given. Surgery was performed 3 months later and follow-up continued for 6 months. Pain severity decreased during the treatment by 30% in both the placebo and infliximab groups. However, no effect of infliximab was observed for any of the outcome measures. After surgery, pain scores decreased in both groups to less than 20% of the initial value. Infliximab appears not to affect pain associated with deep endometriosis.
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In conclusion, there is no enough evidence to support the use of anti-TNF-alpha drugs in the management of women with endometriosis for the relief of pelvic pain (65). No evidence of clinical benefits of infliximab was found for endometriotic lesions, dysmenorrhea, dyspareunia or pelvic tenderness.

Several cytokines may also play a role in the treatment of endometriosis. A major function of interleukin-12 (IL-12) and IL-18 is the regulation of the adaptive immune response (66). IL-12 induces other cytokines, particularly interferon-γ (IFN-γ), which coordinate the ensuing immune response. Intraperitoneal injection of IL-12 in a murine model of endometriosis demonstrated a significant reduction of ectopic endometrial implantation (67).

Pentoxifylline, a phosphodiesterase inhibitor, is the first immune-modulator agent investigated for the treatment of endometriosis (68). Pentoxifylline inhibits phagocytosis and generation of toxic oxygen species and proteolytic enzymes by macrophages and granulocytes in vitro and in vivo. Moreover, pentoxifylline inhibits both TNF-α production by macrophages, and the proinflammatory action of TNF-α and IL-1 on granulocytes in vitro. One randomized controlled trial evaluated the effect of pentoxifylline on future fertility in infertile women with asymptomatic minimal or mild endometriosis (69). Patients were allocated to receive either a 12 month course of oral pentoxifylline (800 mg/day) or an oral placebo. The 12 month actuarial overall pregnancy rates were 31 and 18.5% in the pentoxifylline and placebo groups respectively. However, this difference was not statistically significant. Therefore, there is no evidence from this study that immunomodulation with pentoxifylline aids fertility in those women with minimal or mild endometriosis. A Cochrane systematic review to determine the effectiveness and safety of pentoxifylline, in the management of endometriosis in subfertile women with asymptomatic minimal or mild endometriosis (69). Patients were allocated to receive either a 12 month course of oral pentoxifylline (800 mg/day) or an oral placebo. The 12 month actuarial overall pregnancy rates were 31 and 18.5% in the pentoxifylline and placebo groups respectively. However, this difference was not statistically significant. Therefore, there is no evidence from this study that immunomodulation with pentoxifylline aids fertility in those women with minimal or mild endometriosis. A Cochrane systematic review to determine the effectiveness and safety of pentoxifylline, in the management of endometriosis in subfertile women showed that pentoxifylline had no significant effect on reduction of pain (70). There was no evidence of an increase in clinical pregnancy events in the pentoxifylline group compared with placebo.

In conclusion, there is no enough evidence to support the use of pentoxifylline in the management of premenopausal women with endometriosis in terms of subfertility and relief of pain outcomes. Further studies including more infertile patients with endometriosis are desirable.

10. Others

10.1. Matrix metalloproteinase (MMP)

The MMPs are a family of endopeptidases that are capable of degrading components of the extracellular matrix. It is important to many physiological and pathological processes, including embryo implantation, cyclic endometrial breakdown and endometriosis, and is regulated by its natural occurring inhibitor, tissue inhibitors of matrix metalloproteinase (TIMPs) (71). Suppressing the action of secreted MMPs from human ectopic endometrium with TIMP-1 significantly inhibited the establishment of endometriosis lesions in a nude mice model (72). Doxycycline (Dox) has a number of non-antibiotic properties. One of them is the inhibition of matrix metalloproteinase (MMP) activity. Recent study assessed the effects of Dox in a rat endometriosis model (73). Treatment with Dox caused significant decreases in the implant areas compared with the controls. Low-dose Dox caused regression of endometriosis in experimental rat model.

10.2. 5-Fluorouracil

Recent study investigated the effects of anti proliferative drugs (anastrozole, methotrexate, and 5-fluorouracil [5-FU]) on the proliferation of endometriotic cells in vitro and in vivo (74). Although anastrozole, methotrexate, and progesterone were ineffective, 5-FU significantly decreased the proliferation of endometriotic cells in vitro and controlled the growth of both cells from ovarian endometrioma and deep infiltrating endometriosis. Considering common features between endometriotic cells and tumor cells, the use of 5-FU could be an option in the management of severe endometriosis.

10.3. Thiazolidinediones

Thiazolidinediones (TZDs) do not impede conception and have been shown to reduce endometriotic lesions in animal models. One human study evaluated the effectiveness of a TZD in treating endometriosis-related pain. Participants were given rosiglitazone, 4 mg daily, for 6 months (75). Two of the 3 patients exhibited improvement in severity of symptoms and pain levels with a concurrent decrease in pain medication, while one experienced no change. Rosiglitazone was well tolerated by all patients. Combined with data gathered from studies in rats and nonhuman primates, the results from this study offer positive justification for using TZDs as a well-tolerated treatment for endometriosis that can address pain without impeding ovulation and without the need for add-back therapy.

10.4. Metformin

In a rat model, Oner et al. (76) found that metformin and letrozole caused a statistically significant regression of endometriotic implants. Metformin suppresses the inflammatory response, the activation of aromatase enzyme and the proliferation in endometriotic stromal cells after culture in a sterile medium (77). In human, metformin 500 mg three times daily for 6 months resulted in a significant reduction in the patient's complaints ($P < 0.01$) and in the serum levels of IL-6, IL-8 & VEGF, suggesting that it may have a therapeutic potential as an anti-endometriotic drug (78).

Conflict of interest

The author declares that there is no conflict of interest.

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