Selective progesterone receptor modulators and their use within gynaecology

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Accepted on 24 September 2013

Key content

- Mifepristone, a progesterone receptor antagonist, was initially discovered in the 1980s and has been licensed for use in medical termination since 1991. Subsequently, selective progesterone receptor modulators (SPRM), which have both agonist and antagonist properties, have been developed and have therapeutic advantages over alternative therapies.
- Ulipristal acetate, a SPRM, was licensed as emergency contraception in 2009 and, in May 2012, as a preoperative treatment for fibroids. There is ongoing research on its use for the long-term management of uterine fibroids.

Learning objectives

- History of the development of SPRM.
- Mechanism of action of SPRM.
- Summary of research on ulipristal acetate for the management of fibroids.
- Potential advantages of SPRM over the current medical treatments for uterine fibroids.
- Current licensed uses for ulipristal acetate.
- Potential uses of SPRM in other gynaecological conditions.
- Risks and side effects of SPRM.

Keywords: emergency contraception / selective progesterone receptor modulators / ulipristal acetate / uterine fibroids

Please cite this paper as: Murdoch M, Roberts M. Selective progesterone receptor modulators and their use within gynaecology. The Obstetrician & Gynaecologist 2014;16:46–50.

Introduction

Mifepristone, a progesterone receptor (PR) and glucocorticoid receptor (GR) antagonist, was discovered in 1981 in the course of attempts to develop glucocorticoid receptor ligands.1 The effects it had on menstruation and the ability to interrupt pregnancy eventually led to the development of further compounds with both agonist and antagonist properties on the PR and fewer antiglucocorticoid properties. These compounds are classified as selective progesterone receptor modulators (SPRM).2 SPRMs have been shown to have an antagonistic effect on endometrial and breast tissue PRs without influencing the effect of estrogen on endometrial and breast tissue.3

Mifepristone and ulipristal acetate are the only SPRMs currently licensed for use in the UK, however, other SPRMs have been or are currently being developed and undergoing trial.5 There have been several review articles on the clinical uses of SPRMs.1,2,4 The authors summarise the current licensed uses and potential uses of SPRMs in gynaecology.

Mechanism of action

Progesterone is a steroid hormone synthesised by the corpus luteum of the ovary, the placenta, and also by the adrenal cortex and testes. It prepares the endometrium for pregnancy, maintains the uterus throughout pregnancy and promotes breast development.5 PRs are present, but not exclusively, in endometrial, myometrial and breast tissue. Progesterone enters the cytoplasm of the cell where it binds to the PR. Dimerisation results in formation of the progesterone receptor complex. This complex then binds to the basal transcription apparatus in the nucleus via co-activators and initiates transcription of the target gene.1 PR agonists initiate transcription via co-activators and PR antagonists inhibit transcription via co-repressors.1,4 There are two isoforms of the PR, human progesterone receptor A (hPR-A) and human progesterone receptor B (hPR-B). They differ in that the hPR-B has an extended N-terminal region.3,4 Research in mice has demonstrated the different biological effects of activation of these two isoforms.

Activation of the hPR-A counteracts estrogen induced endometrial proliferation whilst activation of the hPR-B principally relates to proliferation and differentiation in the mammary gland.3,4 The mechanism of action of SPRMs is not clearly understood.1 It is known that SPRMs bind to both isoforms of the PR producing a mixed agonist and antagonist effect via the combined activation of co-activators and co-repressors.
Uterine fibroids and SPRMs

Uterine fibroids (leiomyomas or myomas) are benign tumours of smooth muscle cells and fibrous tissue that develop within the wall of the uterus. They are the most common tumours of the female genital tract present in 20–40% of women in the reproductive age group. There is increasing evidence that progesterone and the PR have a major role in the growth and development of uterine fibroids. In the management of fibroids an SPRM is required that selectively acts as a progestogen on the endometrium and an anti-progestin within the fibroid.

Fibroids can be asymptomatic or result in abnormal uterine bleeding, urinary incontinence or frequency, pelvic pressure or pain, infertility, miscarriage and pregnancy complications. Treatment is often only required if the woman is symptomatic and is dependent on symptoms. If the woman has heavy menstrual bleeding, the National Institute for Health and Care Excellence (NICE) recommends consideration of pharmaceutical treatment when fibroids are less than 3 cm in diameter and causing no distortion of the uterine cavity. The management of heavy menstrual bleeding is well documented elsewhere and therefore not covered in this article.

Medical management of fibroids

Gonadotrophin-releasing hormone analogues (GnRH-a) are an effective treatment but long-term use is limited due to adverse side effects. These include hot flushes, vaginitis, sweating, change in breast size and bone density loss. The sole use of GnRH-a is generally only considered when all other treatment options, including surgery or uterine artery embolisation (UAE), are contraindicated.

SPRMs could provide a pharmacological treatment option for the long-term management of uterine fibroids if safety and efficacy is confirmed. Within this context, the SPRM of choice should be one that selectively acts as a progestogen on the endometrium and an anti-progestogen within the fibroid. The PEARL group is currently conducting a Phase III multicentre, randomised, double-blind clinical study, investigating the efficacy and safety of repeated 12-week courses of daily ulipristal acetate for this purpose. The study is due to be completed late 2014.

Preoperative medical treatment for fibroids

The current nonpharmacological treatment options include UAE, myomectomy (including transcervical resection) and hysterectomy. Other treatments such as magnetic resonance (MR) image guided percutaneous laser ablation and MR image guided transcutaneous focused ultrasound for uterine fibroids may be available under research conditions.

Preoperative treatment with GnRH-a is recommended in women with a greatly enlarged uterus, preoperative anaemia, or where reduction in fibroid volume may result in a low transverse rather than midline incision. There is evidence demonstrating a significant reduction in uterine volume and fibroid size, a slight improvement in haematological indices, and a possible reduction in intraoperative blood loss and operating time with the preoperative use of GnRH-a. These advantages, along with a reduction in analgesia requirements and length of hospital stay, may also be seen if the use of GnRH-a allows a laparoscopic rather than open procedure. The use of GnRH-a is contraindicated prior to UAE due to the effect it has on blood vessels which complicates the procedure. SPRMs currently offer an alternative preoperative treatment option and are possibly suitable for use prior to UAE.

A recent randomised, parallel group, double blind, placebo controlled phase III trial (PEARL I) evaluated the efficacy and safety of oral ulipristal acetate versus placebo for the treatment of symptomatic uterine fibroids before surgery. Patients eligible for surgical treatment of fibroids were randomised to receive up to 13 weeks of treatment with ulipristal acetate, 5 mg or 10 mg, or a placebo. The primary end points were a reduction in uterine bleeding and fibroid volume. Menstrual bleeding was controlled in 91% and 92% of women who received 5 mg and 10 mg of ulipristal acetate, respectively and with only 19% in those who received placebo (P <0.001). Median changes in total fibroid volume were −21%, −12% and +3% (P = 0.002 ulipristal acetate 5 mg versus placebo, and P = 0.006 ulipristal acetate 10 mg versus placebo). Although the most common side effects were headache and breast pain, there was no significant difference between ulipristal and placebo groups for discomfort or tenderness in those areas. A low rate of hot flushes was reported in all groups. In contrast to that seen in women treated with GnRH-a, there was no suppression of estradiol in the women treated with ulipristal acetate. The same group conducted a double-blind, double-dummy phase III trial comparing...
ulipristal acetate with leuprolide acetate (injectable GnRH-a) (PEARL II). They reported moderate to severe hot flushes in 11% and 10% of those receiving 5 mg and 10 mg of ulipristal acetate respectively and in 40% of those receiving leuprolide acetate.14 These trials demonstrated ulipristal acetate to be an effective alternative to GnRH-a as a preoperative treatment for women undergoing surgery for uterine fibroids with a reduced side-effect profile.

Although 3-monthly intramuscular preparations of GnRH-a are available, the lack of enteric options is a disadvantage which is overcome by the SPRM ulipristal acetate, which is effective as an oral medication.

Ulipristal acetate (5 mg daily Esmya® [Gedeon Richter, Budapest, Hungary]) is currently licensed for the preoperative treatment of uterine fibroids, with treatment duration limited to 3 months. The Faculty of Sexual and Reproductive Healthcare advise against the use of concomitant progestogens, as the competitive action on the PR is likely to reduce efficacy. Although most women will be amenorrhoeic, for the same reasons as for those on GnRH-a, nonhormonal contraception is advised.15,16

Contraception and SPRMs

SPRMs inhibit or delay ovulation by blocking the luteinising hormone (LH) surge and follicular rupture whilst maintaining plasma estrogen levels.1,17 These effects have been demonstrated with the SPRMs asoprisnil, mifepristone and ulipristal acetate.1,4 SPRMs also have a direct effect on the endometrium (discussed below) which may have an effect on implantation.1

In the UK, mifepristone, in combination with a prostaglandin, has been licensed for use in medical termination of pregnancy (TOP) since 1991, with a complete TOP rate of at least 95%.18

A double-blind randomised control trial of 2 mg and 5 mg of mifepristone taken for 120 days showed that it inhibited ovulation, induced amenorrhoea and potentially prevented pregnancy.2,19 A randomised non inferiority trial comparing the efficacy and safety of ulipristal acetate with that of the progesterone levonorgestrel (LNG) for emergency contraception concluded that ulipristal acetate is an effective alternative which can be used for up to 120 hours after unprotected sexual intercourse (UPSI).20 A significantly lower pregnancy rate was observed in women given ulipristal acetate when compared to the LNG in all time periods up to 120 hours. A Cochrane systematic review concluded that mid-dose mifepristone (25–30 mg) is superior to LNG and that ulipristal acetate may be more effective than LNG.21

There are three methods of emergency contraception licensed for use in the UK; ulipristal acetate, LNG and the copper-bearing intrauterine device (Cu-IUD). Ulipristal acetate (30 mg single dose Ellaone®[HRA Pharma, Paris, France]) and the Cu-IUD can both be used up to 120 hours after UPSI or contraceptive failure. Ulipristal acetate is the only oral method licensed for use between 72 and 120 hours of UPSI.17

Whereas LNG can be used to cover UPSI more than once in a cycle ulipristal acetate is only licensed to be given once.17 Both LNG and ulipristal acetate may interfere with the efficacy of hormonal contraceptive methods. It is recommended that subsequent acts of unprotected sexual intercourse be protected with barrier methods until the next menstrual period starts.15

Due to the anovulatory effects of SPRMs they also have the potential to be used as long term contraceptives potentially suitable for use in women in whom contraceptives are contraindicated. Irregular bleeding is experienced in up to 70% of women taking the progesterone only pill (POP) and between 10% and 25% discontinue POPs within a year due to this side effect.22 SPRMs induce amenorrhoea, although the exact mechanism behind this is unknown.1 Amenorrhoea rates of up to 70% with ulipristal, 70% with asoprisnil and 90% with mifepristone have been observed.13,19,23 Preliminary data from ongoing trials of ulipristal acetate have suggested a higher amenorrhoea rate. SPRMs may offer an effective long-term contraceptive without the undesirable side effect of irregular bleeding. Mifepristone has been considered and researched for use as a long-term contraceptive for many years but it is not established or licensed for this use within the UK.24

Endometriosis and SPRMs

Endometriosis is defined as the presence of endometrial like tissue outside the uterus, which induces a chronic, inflammatory reaction.25 It is a common condition causing symptoms such as dysmenorrhoea, dyspareunia, pelvic pain, dyschezia and infertility.25 One of the current pharmacological treatment options is based on the suppression of ovulation, which is shown to reduce pain associated with endometriosis. These include the combined oral contraceptive pill, danazol, gestrinone, medroxyprogesterone acetate and GnRH-a.25 The LNG–IUS has also been shown to reduce pain associated to endometriosis.25 All have various contraindications, side effects and limitations, which have been discussed previously. When using GnRH-a, a regime of ‘add back’ hormone therapy is recommended.10 Surgical excision or bilateral salpingo oophorectomy (+/- hysterectomy) is not always appropriate, especially for women who wish to retain fertility.1

SPRMs may offer a pharmacological therapeutic alternative potentially improving the symptoms of endometriosis by the suppression of ovulation, antiproliferative effects on the endometrium and suppression of endometrial bleeding.2

Small studies on the effects of mifepristone have demonstrated improvement in pelvic pain and uterine
cramping associated with endometriosis, along with a regression of endometriosis.\textsuperscript{14,26} Short courses of asoprisnil versus placebo have been shown to be effective in reducing nonmenstrual pain and dysmenorrhoea in women with a laparoscopic diagnosis of endometriosis.\textsuperscript{1–3} The effects of SPRMs on the endometrium limit their long-term use and are currently being evaluated. The effects on ectopic endometrium are unknown.\textsuperscript{1,4}

**Other potential uses of SPRMs in gynaecology**

The role of SPRMs in the management of dysfunctional uterine bleeding is yet to be defined. As discussed earlier SPRMs induce amenorrhoea with very few reports of breakthrough bleeding.\textsuperscript{5}

**Limitations of SPRMs**

**Risk of endometrial cancer**

Unopposed estrogen is a well documented risk factor for endometrial cancer and therefore the effects of endometrial PR antagonists in premenopausal women are a safety concern.\textsuperscript{27} Endometrial changes unique to progesterone receptor modulators (PRM) are described and referred to as PRM-associated endometrial changes (PAEC).\textsuperscript{27} These newly described non-physiological changes are generic and not specific to a single PRM. SPRMs have different agonist and antagonist properties and therefore variable effects on the endometrium. Although glandular changes consistent with concurrent estrogen and progesterone stimulation are distinctive they are not always present. It is therefore not always possible to identify patients taking PRM on histology alone and it is therefore important to inform the pathologist when sending a hysterectomy or an endometrial biopsy specimen.\textsuperscript{17,27}

PAEC were evaluated in women taking short courses of SPRMs (asoprisnil, ulipristal acetate and telapristone acetate) and no hyperplasia, premalignant or malignant lesions were identified in these specimens.\textsuperscript{4,13,27} Due to the theoretical concerns, however, the use of ulipristal acetate is currently limited to 3 months. The effects of ulipristal acetate on the endometrium were assessed in the PEARL trials.\textsuperscript{13,28} Although nonphysiological changes were seen frequently in the ulipristal group, these changes had resolved 6 months after treatment demonstrating reversibility of these changes and safety in this respect of their short-term use.\textsuperscript{19} Further research on the long term PAEC are required before they can be safely used for a prolonged duration.

At present, there do not appear to be any significant side effects of ulipristal acetate but it is recommended that they be used with caution in those with severe asthma uncontrolled by oral glucocorticoids and in those with hepatic dysfunction, hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.\textsuperscript{4,17}

**Breast tissue and SPRMs**

The Women’s Health Initiative study and the Million Women Study have both demonstrated an increased risk of breast cancer in women taking both combined and estrogen-only hormone replacement therapy. SPRMs may have a potential role in the treatment of women with breast cancer and possibly a preventative role in the development of breast cancer in high risk groups such as those with BRCA gene mutations. This is being actively researched.\textsuperscript{1}

**Conclusion**

We are still in the early days of realising the full potential of SPRMs. The benefits of mifepristone are widely appreciated and it has thus been accepted in gynaecological practice. Ulipristal acetate is readily available as an emergency contraception and within the last year, it has been licensed for preoperative use in the management of uterine fibroids. The science behind the progesterone receptor is still being explored and the development of further SPRMs is likely to continue with exciting prospects for use within gynaecology.

It is also important to remember that progesterone receptors are present in other tissues in the body and therefore their use is not just limited to those within gynaecology.

**Disclosure of interests**

Mark Roberts is a Principle Investigator for the PEARL IV study sponsored by PregLem S.A. a member of the Gedeon Richter Group.

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