Progesterone receptor modulators in gynaecological practice

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Introduction

The sex steroid progesterone plays a major role in the regulation of female reproductive activity. Circulating levels of progesterone are maximal in the secretory phase of the menstrual cycle, its main source being the corpus luteum. The effects of progesterone are mediated via the progesterone receptor (PR), which is essential not only for the co-ordination of ovulation, implantation and the maintenance of pregnancy but also for breast development and sexual behaviour. Within the uterus, progesterone predominantly contributes to the regulation of endometrial function. Progesterone is crucial in preparation for implantation by decidualisation, during pregnancy and during the process of menstruation, which occurs when progesterone levels fall in the absence of a conceptus. Since the discovery of natural progesterone in the mid-1930s,¹ many synthetic progestogens have been developed and introduced into clinical practice. As contraceptive agents, these compounds have revolutionised fertility control. Progestogens also have an established role in the management of benign gynaecological conditions such as menstrual disturbances and endometriosis, as well as in hormone replacement therapy and assisted reproductive technology.

The discovery of the progesterone receptor^{2,3} enabled the development of synthetic compounds binding to the PR with agonistic but also with antagonistic properties. The first of these to be described in 1981 was mifepristone (RU 486), a PR and glucocorticoid receptor (GR) antagonist.⁴ Reports soon followed on its effect on menstruation,⁵ highlighting its potential for cycle regulation and birth control.⁶ It was established that mifepristone could induce menstruation by interrupting the luteal phase of the menstrual cycle. Its potency to disrupt early pregnancy was then recognised, leading to its clinical application in the termination of pregnancy.⁷ Various related compounds exerting their effect via the PR have subsequently been developed and are reviewed here.

Development of PRMs

The initial aim in developing progesterone receptor modulators (PRMs) was to find compounds with more profound P antagonistic potency but less antiglucocorticoid activity than mifepristone. The applications envisaged in the early stages were fertility control and the treatment of breast cancer.^{8,9} The major therapeutic potential of PRMs for the management of benign gynaecological conditions became apparent when their endometrial antiproliferative effect inducing endometrial atrophy and amenorrhoea was

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Correspondence to: Professor Hilary Critchley, University of Edinburgh Centre for Reproductive Biology, Queens Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK. E-mail: Hilary.Critchley@ed.ac.uk demonstrated, initially in non-human primates and rabbits.^{10,11} Unfortunately, the significant abortifacient activity of progesterone receptor antagonists (PAs) led to the delay and obstruction of development of mifepristone and similar compounds with progesterone antagonistic properties for other clinical applications. Large pharmaceutical companies distanced themselves from the perceived negative image of a drug that was capable of terminating a pregnancy. Further introduction of PRMs into clinical practice was also precluded by concerns regarding safety of the endometrium, as it may potentially be exposed to the effects of unopposed estrogens, and concerns regarding their antiglucocorticoid activity at higher doses.

A drug discovery programme was initiated to develop a compound with partial PR agonistic and antagonistic properties on the assumption that this would eliminate the concerns regarding PRMs.¹² A number of compounds with varying degrees of PR agonist and antagonist properties were synthesised (Figure 1) and those with partial and mixed agonist/antagonist activity were classified as selective progesterone receptor modulators (SPRMs). These demonstrated high PR binding affinity and PR specificity with much reduced antiglucocorticoid activity compared to mifepristone. Their more favourable effect on the endometrium was attributed to their partial PR agonistic activity.^{13,14} The SPRM, asoprisnil (J867), was selected for further clinical development as it demonstrated particularly pronounced PR agonistic properties and absence of labour-inducing or abortifacient activity.12

Many potential indications for PRMs in benign gynaecology have been proposed including the management of menstrual disturbances, uterine fibroids and endometriosis.^{15,16} Most clinical experience to date has been with asoprisnil and mifepristone. Randomised double-blind placebo-controlled trials have also been conducted with ulipristal (CDB-2914) and proellex (CDB-4124).¹⁷ For many years, mifepristone was the only compound licensed for clinical use. Recently, ulipristal has received a licence for emergency contraception.^{18,19}

A number of other PRMs have been developed including onapristone, Org 31710, Org 33628, ZK 137 316, ZK 230 211 among others. Preclinical^{20–23} and clinical²⁴ studies have been published with findings of dosedependent suppression of menstrual and ovarian cyclicity.^{21,23} Profound reduction of menstrual blood loss has been demonstrated consistently. Studies in macaques have been conducted with ZK 230 211 administered via an intrauterine system (IUS) with similar results.²² The use of ZK230 211 administered via an IUS in humans with a view to its potential in contraception and in the management of benign gynaecological conditions has been evaluated in one pilot study.²⁴ This study demonstrated that intrauterine delivery of ZK 230 211 is feasible, as significant endometrial levels of the drug were detected.

This review focuses on the evidence for the use of the PRMs that have been administered in clinical trials to date.

Endometrial effects of PRMs

The discovery of the endometrial antiproliferative effect of PRMs was an important milestone in their development.^{11,25} It was also unexpected, as compounds



with PR antagonistic activity had been anticipated to result in unopposed estrogenic effects on the endometrium. A number of studies had described a significant proportion of women developing endometrial hyperplasia when mifepristone was used for the management of uterine fibroids at doses of 5-50 mg daily for 3-6 months.²⁶⁻²⁸ A report was also published of significant endometrial hyperplasia following 6 months courses of mifepristone at 400 mg per day.²⁹ On further histological examination, however, in most cases the changes described as hyperplastic consist of cystically dilated glands,³⁰ which contrary to the glands in endometrial hyperplasia, do not exhibit increased mitotic indices. There have been no reports of cytological atypia. Administration of mifepristone in low doses (2–5 mg) for 120 days has been reported to reduce endometrial proliferation markers.³¹ Asoprisnil has not been found to cause endometrial hyperplasia after administration for up to 12 weeks. A study into the effects of 10 or 25 mg asoprisnil given for 12 weeks on endometrial proliferation markers demonstrated that asoprisnil does not induce proliferation, and indeed the stromal expression of the proliferation marker Ki-67 was significantly decreased. In addition, the expression of the tumour suppressor gene PTEN, previously described as a gatekeeper of endometrial carcinogenesis,32 was unaffected and specifically not suppressed.33

It has now been recognised that the endometrial morphological features described with PRMs are a unique class effect and are not consistent with the previously recognised histological changes through the normal cycle.^{34,35} New diagnostic criteria to describe the features observed with PRM administration have been developed with the intention of raising the awareness of pathologists when assessing endometrial morphology after exposure to this class of compound.³⁶ To date, no pre-malignant lesions have been described.

Potential clinical applications for PRMs Heavy menstrual bleeding

Menstrual disturbances have an impact on the quality of life of many women. The prevalence of menstrual complaints has increased over the last century with earlier menarche, increased life expectancy, advances in fertility control and shorter episodes of lactational amenorrhoea.

Examples of selective Figure 1 progesterone receptor modulators (SPRMs) exhibiting varying degrees of progesterone receptor (PR) agonist and antagonist properties, including those with partial and mixed agonist/antagonist ONA, onapristone; RU486, ne; J867, asoprisnil. Figure activity. mifepristone; reproduced, with permission, from Schubert G, Elger W, Kaufmann G, Schneider B, Reddersen G, Chwalisz K, Discovery, chemistry, and reproductive pharmacology of asoprisnil and related 11beta-benzaldoxime substituted selective progesterone receptor modulators (SPRMs). *Semin Reprod Med* 2005; **23**: 58–73. © Thieme Medical Publishers

With the current trend for women to postpone plans for a family to their fourth or even fifth decade, surgical intervention is often not an option. Hence, there is an increasing requirement for an acceptable form of medical management.^{37,38} Suppression of menstruation may be desirable not only for women suffering from excessive menstrual blood loss but also as a personal option for any woman between menarche and menopause. The perceived benefits of amenorrhoea include the abolition of heavy blood loss and painful periods and a reduced risk of anaemia. A questionnaire survey of 1001 women attending a family planning clinic showed that the reduction of periods associated with certain forms of contraception was highly acceptable.³⁹ It has even been argued that menstruation should be optional for all women.^{40–43} PRMs may offer this option once it has been established that longterm administration is safe.

The medical management options for heavy menstrual bleeding (HMB) have been reviewed previously.44 Currently, most involve the administration of progestogens, either orally, parenterally or via an IUS. The side effect most commonly responsible for discontinuation of such therapy is unscheduled bleeding. Most studies assessing the effect of PRMs on bleeding pattern have been carried out in patients with benign uterine pathology such as uterine fibroids, which are known to contribute to the symptom of HMB. However, the effect of asoprisnil was also evaluated in 60 women with regular menstrual cycles and no uterine pathology in a Phase I double-blind dose-escalation study. They were administered doses of asoprisnil varying from 5 mg once daily to 50 mg twice daily for 28 days commencing during the first 4 days of their cycle. As a result, cycle lengths were increased, and the onset of menstruation was significantly delayed with doses at or above 10 mg once daily.⁴⁵ Suppression of menstruation with asoprisnil has been found to be reversible and not associated with the adverse systemic side effects of estrogen deprivation as seen gonadotropin-releasing with hormone (GnRH) analogues.^{12,46} The prolongation of the menstrual cycle in this Phase I study occurred even in the presence of a normal luteal phase and luteolysis, indicating that the endometrium is a direct target.⁴⁵ Asoprisnil may have clinical advantages over continuous progestogen treatment, as reports of unscheduled bleeding with PRMs have been rare.

Uterine fibroids

Current options of medical management for symptoms associated with uterine fibroids are very limited due to unfavourable success rates and side effect profiles. HMB is the commonest symptom requiring intervention and is often refractory to administration of progestogens, particularly if the uterine cavity is enlarged and distorted. Any symptoms due to the mass of the fibroids such as pelvic pressure or discomfort are even less amenable to pharmacological intervention. GnRH analogues may only be administered on a temporary basis due to their hypoestrogenic side effects. Uterine artery embolisation (UAE) is a potentially fertility-conserving and non-surgical management option and has recently been compared to hysterectomy with favourable results.⁴⁷ Longer-term follow-up studies of UAE, particularly regarding its effect on subsequent pregnancies, are awaited.

PRMs may prove to be an important advance in the medical management of symptomatic uterine fibroids as the clinical effects of this class of compounds are dramatic.^{48,49} In addition to their beneficial effect on bleeding patterns, PRMs reduce the size of the fibroids and therefore have the potential to alleviate symptoms due to fibroid mass. Favourable results have been reported in studies that included assessments of the impact on patients' leiomyoma-specific quality of life.^{50,51}

Mifepristone has been described to significantly improve bleeding patterns in women with uterine fibroids. Reports of amenorrhoea vary and appear to be dose dependent, but range from 60-100% with doses of 5-50 mg daily.^{26–28,52} A recent study using a low dose of 5 mg mifepristone for 6 months found an amenorrhoea rate of 41%.⁵¹ Other fibroid-related symptoms such as dysmenorrhoea and pelvic pressure have also been seen to respond favourably to the administration of mifepristone.²⁷ Reduction in the size of fibroids by 26-74% has been described with administration of 5-50 mg mifepristone once daily for 3-6 months.²⁷ The evidence regarding the dose dependency of this effect is currently inconclusive. Whilst no consistent correlation between dose and response could be found in one review,²⁷ a study specifically investigating the dose-response effect concluded that only doses of at least 25 mg daily achieved a clinically significant decrease in fibroid volume.⁵³ The reduction in the size of fibroids may also be related to the duration of exposure to mifepristone.²⁷ Recent randomised placebocontrolled trials in women with symptomatic fibroids have reproduced the findings of decreased fibroid volumes and a significant reduction in menstrual blood loss, resulting in increased haemoglobin levels after treatment with 5-50 mg mifepristone once daily for 3-6 months.^{28,30,51}

Phase II studies with asoprisnil in women with uterine fibroids reaffirmed the observation that this compound induces reversible amenorrhoea. In a double-blind, placebo-controlled study, doses of 5, 10 or 25 mg of asoprisnil were administered orally to women with uterine fibroids for 12 weeks.⁵⁴ Duration and intensity of uterine bleeding were significantly reduced in a dose-dependent manner, and no episodes of unscheduled bleeding were reported. Amenorrhoea was achieved in over 83% of patients with the highest dose of 25 mg. In addition to the suppression of both normal and heavy menstrual bleeding, a reduction in the volume of the largest fibroid (by 36%) after 12 weeks with 25 mg asoprisnil) was demonstrated, resulting in a dose-dependent improvement of pressure symptoms such as bloating and pelvic pressure.^{48–50} In a subsequent and similar double-blind, placebo-controlled study with 10 or 25 mg of asoprisnil for 12 weeks, these findings were reproduced with a particularly impressive

reduction in menstrual blood loss, a decrease in fibroid size and a significant improvement in quality of life.⁵⁰ In this study, the menstrual blood loss was semi-quantitatively assessed with a menstrual pictogram, which showed that between the pre-treatment cycle and the final month of treatment there was a difference in blood loss of -154 and -215 ml in the 10 and 25 mg asoprisnil groups, respectively. Considering the traditional definition of HMB as menstrual loss over 80 ml,⁵⁵ this was a dramatic improvement. Even in this cohort of women presenting with excessive menstrual bleeding, amenorrhoea was achieved in 91% of patients with a daily dose of 25 mg asoprisnil.

The effect of CDB-2914 administered for 3 months in doses of 10 and 20 mg to women with symptomatic fibroids has been evaluated in a randomised, placebocontrolled trial. The higher dose of 20 mg achieved amenorrhoea in all patients. As well as suppression of menstruation and ovulation, CDB-2914 was found to significantly reduce fibroid volumes by 21–36% and to improve quality of life, comparable to the results of studies with other PRMs.⁵⁶

The mechanism of the effect of PRMs on fibroid size has not yet been fully elucidated. Reduced uterine artery blood flow in women with symptomatic uterine fibroids has been described with both mifepristone⁵⁷ and asoprisnil⁵⁰ and may contribute to the decrease in tumour size. Asoprisnil also appears to target uterine leiomyoma cells directly, resulting in restriction of proliferation and induction of apoptosis, whilst leaving normal myometrial cells unaffected.⁵⁸

Endometriosis

As with other benign gynaecological conditions, medical management of endometriosis is currently largely dependent upon administration of progestogens. Estrogen deficiency restricts long-term use of GnRH analogues. Not only is satisfaction with medical management often limited by the side effects, but symptom control may also remain suboptimal.

The results of studies of PRMs in women with endometriosis are promising.^{13,59} Mifepristone has been shown to have a significant beneficial effect on symptoms and extent of disease with administration of 50 mg daily for 6 months.⁵⁹ The rationale for the use of asoprisnil in the management of endometriosis is based on the presumed effects of tissue-selective inhibition of endometrial proliferation and suppression of endometrial bleeding by targeting the endometrial vasculature directly.^{13,49} The finding of tissue-specific suppression of endometrial prostaglandin production in preclinical studies also appeared promising with regard to the potential of asoprisnil to ameliorate endometriosisassociated pain.^{10,60} Phase II studies with asoprisnil have been conducted in women with pelvic pain due to endometriosis. In a randomised, placebo-controlled study, doses of 5, 10 or 25 mg asoprisnil were administered for 12 weeks to women with a laparoscopic diagnosis of endometriosis who suffered moderate or severe pain. All three doses significantly reduced non-menstrual pelvic pain and dysmenorrhoea compared to placebo.49

Contraception

Mifepristone strongly antagonises all effects of progesterone, including endometrial preparation for implantation and maintenance of pregnancy. Hence, not surprisingly, its first clinical application was for termination of pregnancy, which remains its only licensed indication.^{61,62} Mifepristone has also been demonstrated to

act as a highly effective postcoital contraceptive agent. $^{63-65}$ The potential of ulipristal for use in emergency contraception was also explored, and it was found to be at least as effective as the progestogen, levonorgestrel (LNG). 66 Ulipristil has received a product licence for this indication and is therefore the second PRM to become available for clinical use.

The concept of administering mifepristone as an estrogen-free contraceptive pill has also been evaluated.^{67,68} Clinical trials have been conducted administering 2 or 5 mg of mifepristone daily for 4–6 months, demonstrating it to be an effective oral contraceptive agent, inhibiting ovulation and inducing amenorrhoea in the majority of cases.⁶⁹ When compared to progestogen-only pills, the effect on the bleeding pattern was significantly more favourable, with more cases of amenorrhoea and a lower incidence of spotting.⁷⁰ There is a potential for PRMs to be developed for use in fertility control, if their advantages can be more widely appreciated and if they can be divorced from their image as abortifacients.

PRMs have been administered as a therapeutic intervention for the management of unscheduled bleeding with progestogen-only contraception (POC).^{71–73} Breakthrough bleeding is a frequent reason for discontinuing POC.^{74,75} In one study, the discontinuation rate of new users of the LNG-releasing intrauterine system (LNG-IUS) due to bleeding problems was found to be 16.7% over 5 years. As is well known, this side effect is most prevalent during the first months post-insertion and most patients who stop using the LNG-IUS due to unscheduled bleeding do so during the first year (10.5%).⁷⁶ PRMs have been proposed to ameliorate this effect.⁷⁷ Even a single dose of mifepristone (200 mg) has been shown to reduce bleeding episodes in users of a LNG-releasing subdermal contraceptive implant.⁷³ Org 31710 also appeared to regularise the bleeding pattern when administered monthly in addition to a desogestrel-only contraceptive pill.⁷⁸ However, suppression of unscheduled bleeding has not been consistently demonstrated, and the implications for contraceptive efficacy also remain to be clarified.79,80 One study administering CDB-2914 to new LNG-IUS users in an attempt to prevent breakthrough bleeding found that the initial beneficial effect was temporary. With ongoing treatment, the placebo group appeared to have a more favourable bleeding pattern, even though there were no significant differences in acceptability measures.⁷⁹ This study highlighted the important difference between prevention and treatment of an undesired side effect and concluded that there is possibly more potential for PRMs to improve than to prevent unscheduled bleeding in users of POC.79

Other indications

Alternative applications of PRMs beyond the context of gynaecology have also been proposed, either utilising the antiglucocorticoid effects of some compounds, or in non-gynaecological conditions that are sensitive to sex steroids. The use of PAs in the treatment of breast cancer was envisaged very soon after their discovery.⁸¹ Since then, many other applications for PRMs have been considered and reviewed.⁸² Clinical trials have mostly been conducted with mifepristone.

Preclinical and clinical studies exploring the potential of mifepristone for the management of breast cancer succeeded in demonstrating a response of tumour growth inhibition.⁸³ A Phase II study with daily administration of 200 mg mifepristone in women with untreated metastatic breast carcinoma concluded that its use as a single agent could not be supported.84 However, an additive antiproliferative effect was demonstrated when PAs were combined with anti-estrogens such as tamoxifen or with an aromatase inhibitor, suggesting that PRMs may have a place in the endocrine therapy of breast cancer as part of a combination regime.⁸⁵ The potential of PAs for the prevention of breast cancer has also been evaluated. In premenopausal women, the administration of 50 mg mifepristone every other day for 3 months has been shown to block breast epithelial cell proliferation, implying a possible protective effect.⁸⁶ In another study, mice lacking the rodent version of the breast cancer susceptibility gene BRCA1 were given mifepristone, which inhibited mammary tumorigenesis.⁸⁷ The results of these studies appear to support a potential preventive role for PRMs, particularly in women who have been identified as being at increased risk of developing breast cancer.

Mifepristone has also been used in cases of inoperable meningioma after it was established that this tumour type is modulated by female sex hormones and commonly expresses PR.^{88,89} There may be further benefits in the management of other tumour types,⁹⁰ and a response of human ovarian carcinoma cell lines has been reported in an *in vitro* study.⁹¹ Whilst the antiglucocorticoid activity of mifepristone may result in commonly undesired side effects, it also constitutes the basis for its advantages in the management of Cushing's syndrome.^{92,93} Overall, the broad medical applicability of mifepristone has been appreciated for almost two decades, but political issues surrounding its association with termination of pregnancy have hampered further development.⁹⁴

Summary

Preclinical and clinical studies have demonstrated the potential role for PRMs in the management of benign gynaecological conditions. Mifepristone is licensed for use in termination of pregnancy but its potential advantages for use in contraception, management of HMB, uterine fibroids and endometriosis as well as in nongynaecological and oncological conditions have also been highlighted. Further development of related compounds has been obstructed by the controversial political issues regarding their abortifacient properties. The potential of asoprisnil to become a novel treatment for HMB, symptomatic uterine fibroids and endometriosis has been demonstrated and accompanied by a favourable safety and tolerability profile in all clinical studies to date. Ulipristal has recently been licensed for use in postcoital contraception, and the potential applicability of other PRMs has also been explored.

Early studies with mifepristone reported endometrial morphological changes as hyperplastic, but these have subsequently been described in further detail as cystic glandular dilatation without increased mitotic activity. No pre-malignant changes have been reported in response to treatment with PRMs. The unique morphological features demonstrated in endometrium following administration of PRMs are now recognised.³⁶ In the future, it is hoped that long-term studies will confirm the safety as well as the efficacy of these compounds.

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Competing interests The authors had access to the progesterone receptor modulator CDB-2914 for use in a study in women with breakthrough bleeding using a progestogen-releasing IUS.

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