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(11) **SUPERTITLE** SPRM gynaecological use

Gynaecological uses of a new class of steroids: the selective progesterone receptor modulators

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Abstract

Selective progesterone receptor modulators (SPRM) represent a new class of synthetic steroids, which can interact with the progesterone receptor (PR) and can exert agonist, antagonist or mixed effects on various progesterone target tissues *in vivo*. This review evaluates the actual and potential usefulness of SPRMs in gynaecology.

(12) **Keywords:** *???* SPRM, progesterone, progesterone receptor, contraception, therapeutic abortion, endometriosis, myoma, woman, human

Introduction

The progesterone receptor (PR) belongs to the nuclear receptor super family and controls specific genes involved in female reproduction. The primary action of progesterone is to initiate and maintain pregnancy. Progesterone, the natural ligand of the PR, represents the pure agonist, onapristone, mifepristone show a pure antagonist activity and asoprisnil exhibits partial agonist/antagonist effects [1].The synthesis of mifepristone, the first PR antagonist (PA) was a starting point of drug discovery and the research programme in the area of PAs [2–4].

Progesterone is involved in the control of ovulation, facilitating the luteinising hormone (LH) surge.

It transforms the endometrium from a proliferative to a secretory state and, together with estradiol, maintains endometrial integrity [5] preparing the endometrium for implantation. It inhibits uterine contractility [6].

In uterus, progesterone controls the growth and differentiation of endometrial and myometrial cells. During the luteal phase, in the primate uterus, progesterone inhibits estrogen induced mitotic activity in the functional zones of the endometrial epithelium but shows some stimulatory effect on both the basalis and endometrial angiogenesis [7]. Progesterone can also play a key role on growth of benign smooth muscles tumours from uterine myometrium [8–10]. In normal breast epithelial cells, progesterone has important mitogenic properties with a peak of a mitotic activity during the luteal phase [11].

Synthetic progestins administered with estrogen in post-menopausal women are involved in the moderately increased risk of breast cancer [12,13]. In the mammary glands of nulliparous Brca1/p53 deficient mice, the PA mifepristone prevents mammary tumorigenesis [14].

From the physiological properties of progesterone and the pharmacological profile of synthetic progestins, and their possible drawbacks, it appears that the potential advantages and the clinical applications of selective progesterone receptor modulators (SPRMs) are very promising in major public health areas.

Clinical application of the SPRMs

Medical abortion

Mifepristone, the first glucocorticoids, and PA [2], a derivative of norethindrone, alters the endometrium and causes decidual necrosis and trophoblast to

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separate from decidua [2,15–17]. Mifepristone sensitises the pregnant uterus and cervix to endogenous and exogenous prostaglandins, increasing uterine activity and inducing cervical softening. Mifepristone is well absorbed orally and reaches a peak serum concentration in pregnant woman within 2 hours. The pharmacokinetics is similar for any dose over 100 mg. The half-life of mifepristone is approximately 19 hours in pregnant women [16].

Mifepristone used alone with oral doses ranging from 50 to 400 mg allows complete abortion in 60–80% up to 48 days gestation. The addition of small doses of a prostaglandin analogue (such as misoprostol) has a synergistic effect resulting in nearly 100% complete abortion [18,19] with lower doses than those required when the prostaglandin analogue is used alone. Moreover, the addition of mifepristone to misoprostol increases complete abortion at a faster rate up to 63 days gestation [16].

The most commonly used medical abortion regimen worldwide is presently mifepristone followed by a prostaglandin analogue. The FDA-approved regimen consists of 600 mg of oral mifepristone followed by a prostaglandin analogue, usually misoprostol, 36–48 hours later. This regimen has been reported to induce complete abortion in 92–99% women [20–23]. As expected on the basis of its pharmacokinetics, lower doses of mifepristone are equally effective as the 600 mg dose when combined with a prostaglandin analogue [24–26]. In the large trial performed by the World Health Organisation, pregnant women were included up to 63 days gestation and received either 200 mg or 600 mg mifepristone, followed 48 hours later by an oral administration of 400 μg misoprostol. Both groups showed similar complete abortion rates (89 and 88%, respectively) [26]. This efficacy is similar to that of vacuum aspiration. In addition, studies using 200 mg mifepristone combined with 800 μg misoprostol administered vaginally to more than 4000 women also confirmed the efficacy of this low dose of mifepristone [27–29]. The vaginal administration of misoprostol prolongs the efficacy of mifepristone regimens up to 63 days. A shorter interval between the administration of mifepristone and prostaglandin analogue does not impair the rate of abortion [30].

The use of mifepristone between 9 and 13 weeks gestation is equally effective as a cervical primer [31]. Animal studies showed that mifepristone induces collagen remodelling. It caused a decrease in collagen organisation with decreased fibril length and diameter [32]. The prostaglandin analogue, misoprostol, is more commonly used in this indication because it is cheaper and largely available. Nevertheless, bleeding and abdominal pain are decreased with mifepristone compared with misoprostol [31,33].

Mifepristone for second trimester abortion decreases the interval between induction to abortion and increases the success rate. It is administered in either 200 or 600 mg dosing and followed by prostaglandin analogue.

Management of miscarriage

A randomised placebo controlled trial showed that expulsion occurred in 82% of women with first trimester arrested pregnancy, within 5 days after administration of 600 mg mifepristone compared with only 8% of women given placebo but the success rate was comparable with that of a misoprostol used alone [34].

Emergency contraception

Emergency contraception (EC) is a term used to describe a group of methods for preventing an unwanted pregnancy that are administered during the first few days after unprotected intercourse. It can decrease individual woman's pregnancy risks by as much as 89% after a single coitus. EC is an important action for woman giving them a chance to avoid the psychological and physical consequences of unwanted pregnancy including the need for legal or clandestine abortion [35].

Several approaches to EC have been described, including high doses of estrogens, danazol, intrauterine devices, oral contraceptive with estrogen and progestin [36], a progestin alone (levonorgestrel) and SPRMs (mifepristone and VA 2914). The Yuzpe regimen involved the combined use of ethinyl estradiol 100 μg and 0.5 mg of levonorgestrel, repeated once 12 hours apart, with the first dose given within 72 hours of unprotected intercourse. This regimen, which was popular in the late seventies and early eighties, has now been supplanted by a more effective and better tolerated progestin only product, containing levonorgestrel. They were to be used within 72 hours of unprotected inter-course.

PR modulators offer another option for EC. They can maintain efficacy for periods of time, longer than 72 hours in a single dose regimen [37,38]. A higher efficacy of mifepristone compared with the Yuzpe regimen was also observed. Side effects such as nausea, vomiting, headache, dizziness, fatigue, low abdominal pain and hot flushes were observed less frequently in women receiving mifepristone [39]. Lowering the dose of mifepristone from 600 to 10 mg did not significantly impair its effectiveness as an emergency contraceptive [40]. Low doses of mifepristone are associated with less disturbance of the menstrual cycle length. A dose as low as 10 mg seems preferable to the 600 mg dose [38]. This trial also showed that unlike levonorgestrel or Yuzpe

regimen, the efficacy of mifepristone does not appear to decline with increased interval up to 120 h.

Recently, a second generation PR modulator with lower anti-glucocorticoid activity than mifepristone was tested in EC. Participants were randomly assigned to receive a single dose of 50 μg of VA 2914 plus a placebo 12 hours later or two doses of 0.75 mg of levonorgestrel taken 12 hours apart. VA 2914 was at least as effective as levonorgestrel in preventing pregnancy after unprotected intercourse. Lower efficacy with increasing interval between intercourse and EC treatment above 48 hours was observed only with levonorgestrel. In contrast, the effectiveness of VA 2914 did not decline after 48 hours. Adverse effects were generally similar in both treatment groups, but more nausea was observed among the VA 2914 treated women. Nausea, as a side effect, has not been reported in other trials with VA 2914 at higher doses. Moreover, VA 2914 was also effective in preventing pregnancy when administered after ovulation [36]. In both groups, women experienced considerable variation in menstrual cycle length when compared with their reported individual normal cycle length. On average, the onset of menses after EC use was 2, 1 day earlier than anticipated in levonorgestrel users and 2, 6 days later in VA 2914 users [37].

Acceleration of tubal transport of fertilised eggs has been reported in rats exposed to anti-progestogen [41]. No information is available in women. It is well documented, however, that mifepristone does not increase the risk of tubal pregnancy [41,42].

Long-term contraception

PAs and SPRMs do have contraceptive potential possibly, by several mechanisms [5,43]. They inhibit ovulation by blocking the LH surge and can induce endometrial desynchronisation, thereby interfering with implantation. Recently, mifepristone but not levonorgestrel was shown to inhibit human blastocyst attachment to an *in vitro* endometrial three-dimensional cell culture model [44]. High doses of mifepristone may even induce follicular atresia [45].

The threshold dose for ovulation inhibition is 2 mg/day. At a lower dosage, ovulation occurs and the administration of 0.5 mg mifepristone daily or 5 mg weekly is not effective in pregnancy prevention [46,47]. Two-hundred milligrams of mifepristone, administered 48 hours after the LH surge, shows contraceptive efficacy. However, this option is not clinically relevant because the detection of an LH surge routinely is an expensive and an unreliable method [5,47].

Administration of mifepristone, in the late luteal phase, is not effective in pregnancy prevention [48,49].

VA 2914 is an orally active steroidal SPRM which demonstrates potent PA activity *in vivo* and *in vitro* [50] with a reduced anti-glucocorticoid activity compared with mifepristone [51]. This compound shows anti-ovulatory activity and post-coïtal antifertility activity in rats [52].

We evaluated ovulation inhibition by VA 2914 in women, in a continuous regimen of administration of 2.5, 5 and 10 mg/day for 3 months. We also examined the endometrial impact in each group.

Anovulation (defined by absence of progesterone above 3 ng/mL) was obtained in nearly 80% women in the 5 and 10 mg/day groups with a high rate of amenorrhea (81.2 and 90%, respectively). Plasma estradiol levels remained in the physiological follicular phase range.

Endometrial histological analysis showed predominantly a pattern of secretory phase. Some cystic glandular dilatations were observed in rare cases. No hyperplasia was detected [53].

We quantified the effects of VA 2914 on endometrial vascularisation, fibrillar matrix and vascular endothelial growth factor (VEGF)-A expression in endometrial biopsies from 41 women before and after 12 weeks treatment. No changes were noted in structure, number and size of endometrial vessels. The collagen network and VEGF-A distribution remained comparable during the luteal phase at baseline and under VA 2914 treatment [54]. From these observations, we conclude that long-term VA 2914 treatment does not result in an endometrial morphology comparable with that induced by a progestin. It thus acts on endometrial cells, in a specific way, which is clearly distinct from that of a progestin.

Treatment of uterine leiomyomata

Uterine leiomyomata, also named fibroids, are benign tumours that occur in up of 35% women above 35 years. They account for up to 40% of all hysterectomies [55]. Non-surgical treatment options for symptomatic leiomyomata are limited because gonadotropin releasing hormone agonists (GnRHa) induce hypo estrogenism and side effects limiting the treatment duration [56]. Even, when a decrease in leiomyomata size of 36% is observed after 12 weeks of GnRHa treatment, the uterus returns to pre-treatment size within 6 months after treatment completion. The indications of GnRHa are thus limited to short-term pre-surgical treatment [57].

Progesterone and PR seem to play a key role in the control of uterine fibroid growth [58]. Mitotic activity is maximal during the luteal phase [59]. Several studies have shown an up-regulation of PR in uterine leiomyomata compared with normal adjacent myometrium at mRNA and protein levels [60]. The expression of the proliferation marker Ki-67 is also

increased in leiomyomata, when compared with that in normal myometrium, and up-regulated by progesterone [60]. Expression of epidermal growth factor, a proliferative cytokine, and Bcl2, an apoptosis-inhibiting protein is also increased in fibroids relative to the adjacent myometrium, specifically during the secretory phase [61]. Progesterone increases Bcl2 protein expression in primary leiomyomata cell cultures [62]. Progestins finally attenuate or even reverse the inhibitory effects of GnRHa on leiomyomata size when used as add-back therapy [63–65]. However, Mifepristone has opposite effects [66] and may decrease proliferation of these smooth muscle cells, suggesting a clinical usefulness of SPRMs for the treatment of myomas. Asoprisnil, a mixed progesterone agonist/PA with no anti-glucocorticoid effect, inhibits proliferation and induces apoptosis in cultured uterine leiomyoma cells in the absence of comparable effects on cultured normal myometrial cells suggesting a cell type specific effect [67].

Down regulation of VEGF, of adrenomedullin, a vasoactive hormone and of their receptors was shown by western blot analysis in cultured human uterine leiomyoma cells treated with VA 2914. This action of VA 2914 was not observed in the surrounding normal myometrial cells, suggesting a cell type specific action of this SPRM on leiomyoma cells [68].

In clinical studies, daily treatment with 5–50 mg mifepristone for 3–6 months resulted in a reduction in uterus and leiomyoma volumes, ranging from 27 to 49% and 26 to 74%, respectively. Moreover, the prevalence and severity of dysmenorrhoea, menorrhagia and pelvis pressure were reduced. Treatment was well tolerated. Nevertheless, endometrial hyperplasia, a serious adverse effect of mifepristone was detected in 28% women [65]. A 20% reduction of myoma volume was also observed in over 90% patients treated with 12.5 mg mifepristone or GnRHa [69]. The recurrence rate after cessation of treatment was 40% after GnRHa and 17.8% after mifepristone [64].

Asoprisnil (5, 10 or 25 mg) given orally, once daily for 12 weeks reduced the uterine volume as well as the volume of the largest leiomyoma in a dose-dependant manner. At 10 and 25 mg, it suppressed pelvis pressure after 12-weeks treatment in contrast to placebo, which was inactive. No decrease of plasma estradiol or increase of cortisol was observed. This treatment is well tolerated and reduces significantly both duration and intensity of uterine bleeding in a dose-dependant manner [70].

Treatment of endometriosis

Endometriosis is an estrogen-dependent disease due to ectopic endometrium. It causes pelvic pain, dyspareunia, dysmenorrhoea and infertility [71]. Pelvic pain is the result of a local inflammatory reaction and up-regulation of cyclooxygenase (COX)- 2. The use of COX-2 inhibitors is therefore an effective symptomatic option [72]. Use of therapeutic agents, which hinder endometriosis, is limited by their side effects. GnRHa and GnRH antagonists use results in a hypo estrogenic state with hot flushes and bone loss, which limits the treatment duration. Progestins, the other therapeutic option, can induce bloating, breakthrough bleeding, mood changes, acne, hirsutism that can alter therapeutic compliance [73].

Inhibiting ectopic endometrium proliferation without inducing estrogen deprivation would be an important goal for the treatment of endometriosis. In this indication, SPRMs may ultimately have an important place. Mifepristone inhibits endometrial cells proliferation by activating the nuclear factor-kappa B signalling pathway [74]. Mifepristone also promotes apoptosis in human endometrial cells by over expression of *Bax*, the apoptosis promoting gene and by down-regulation of the anti-apoptosis gene *Bcl2* [75].

Mifepristone (5 or 50 mg/day for 6 months or 100 mg/day for 3 months) improved the clinical symptoms associated to endometriosis [75]. The 50 mg daily dose elicited a mean 55% regression of visible endometriosis after 6 months of treatment.

Asoprisnil, which inhibits endometrial proliferation and prostaglandin synthesis [76], was studied in subjects with a laparoscopic diagnosis of endometriosis at 5, 10 and 25 mg (versus placebo) for 12 weeks. All doses were significantly effective on pain scores, at all treatment months compared with placebo [70]. The effect on bleeding pattern was also dose-dependent. Asoprisnil was well tolerated in short-term studies, and no serious adverse event was reported during treatment period and follow-up [76].

Conclusion

PAs and SPRMs are largely used for fertility control. They have proven efficacy for abortion and EC. In long-term contraception, they offer an estrogen-free contraception with a better bleeding pattern than that associated with progestins. Because they control the growth of leiomyoma and endometrial cells without inducing an hypo estrogenic state, their use in endometriosis and symptomatic leiomyomata could be promising. Large Phase III trials in patients with menorrhagia associated with uterine fibroids are in progress. Efficacy and safety of long-term administration for management of uterine bleeding, endometriosis and uterine fibroids are actively studied.

On the basis of their pharmacological and clinical features, SPRMs could have in the future important potential implications in women's health care.

Some of them such as asoprisnil and mifepristone inhibit mammary epithelial cells proliferation, in animal models. They might have a key role in the prevention and treatment of benign and malignant breast pathologies.

Some concern appeared initially about endometrial safety because hyperplasia was described on mifepristone treatment. Endometrial biopsies from patients treated with different SPRMs were recently reviewed by a panel of experienced pathologists to develop consensus observations and recommendations [77]. New terminology and diagnostic criteria were defined as PRM- associated endometrial changes. These observations are reassuring as no pre-malignant lesions were seen. However, long-term follow-up is necessary to better define the specific role of this new class of agents as well as of their regimen of administration.

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