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REVIEW

Ulipristal Acetate: a Novel Option for the Medical Management of Symptomatic Uterine Fibroids

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ABSTRACT

Fibroids, the most common tumor in women of reproductive age, impact negatively on women's health and quality of life, and have significant cost implications for their management. The current mainstay treatments are surgical (myomectomy and hysterectomy) and more recently radiological (UAE and focused ultrasound surgery). Hysterectomy is curative but precludes future fertility, whereas the impact of the other treatments on reproduction is uncertain. With women in Western societies deferring childbearing to their 30s and 40s, when fibroids are most symptomatic, there is a pressing need for a uterus-sparing medical therapy that is cheap, effective, and enhances reproductive potential. Serendipity and meticulous translational research has shown that progesterone augments fibroid proliferation, raising the possibility that progesterone receptor modulators could inhibit fibroid growth; this research has culminated in the emergence of ulipristal acetate (UA), a first-in-class, oral selective progesterone receptor modulator (SPRM) that has successfully completed phase III clinical trials. It has been licensed in Western Europe for short-term clinical use prior to surgery, and has shown efficacy with a significant reduction in uterine bleeding, fibroid volume, and improved quality of life, without the side effects associated with other medications such as gonadotropin-releasing hormone (GnRH) agonists. As with all new medicines, there are concerns surrounding UA, not least its effect on the endometrium and the long-term impact on general health and reproduction. Research to date has tended to be industry led, and therefore, there is a need for researcher/clinician-led studies to address the wider issues concerning SPRMs. UA may not turn out to be the "Holy Grail" of medical therapy in the treatment of symptomatic uterine fibroids, but it has rightly given cause for a huge optimism. Further laboratory and clinical

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research into PRMs and related compounds will no doubt lead to more refined medications.

Keywords: Fibroids; Selective progesterone Receptor modulators; Ulipristal acetate; Women's health

BACKGROUND

The Significance of Uterine Fibroids for Women's Health and Health Services

Fibroids are the most common benign tumor in women of reproductive age, with an estimated round-figure prevalence of 50% of all women by the age of 50, although there are well-documented racial differences in prevalence rates [1]. Their significance lies in their negative impact on women's health and quality of life, and cost to the health services. Fibroids are symptomatic in 50% of the women who have them, with the peak incidence of symptoms occurring among women in their 30s and 40s [1]. They can cause menorrhagia and dysmenorrhea, the former being the commonest indication for hysterectomy in the UK and the US, and therefore, of significant cost-implications to health services, while other symptoms include pressure resulting in increased urinary frequency, pelvic pain, and constipation. There are circumstances in which fibroids could compromise reproduction [1, 2], possibly causing subfertility, miscarriage, or complications of pregnancy, such as preterm labor, obstructed labor, or postpartum hemorrhage.

Current Treatment Options for Uterine Fibroids and the Unmet Need

Hysterectomy constitutes a "cure" for fibroid disease, as all symptoms are eradicated and there is no possibility of recurrence of the fibroids. However, hysterectomy is unacceptable to women wishing to preserve fertility. A feature of contemporary lifestyle change is that women are increasingly postponing childbearing to their 30s and 40s [1], the same age range that fibroids peak with regard to their symptomatology. The consequence is that the demand for uterus-preserving therapies will increase. Open abdominal myomectomy remains the mainstay of such therapy, but it is a major operation with associated morbidity and indeed mortality risks, may compromise the very same fertility that it seeks to preserve due to the potential for adhesion formation, and there is a significant risk of recurrence of the disease. In recent years a multitude of additional therapeutic choices have emerged, including laparoscopic and vaginal myomectomy [3, 4], and the radiologic interventions of uterine artery embolization (UAE) [5] and magnetic resonance-guided focused ultrasound surgery (MRgFUS) [6]. None of these therapies is, however, a panacea. There are limitations on the size and number of fibroids that can be treated laparoscopically, and the skills required are not always readily available. These constraints also apply to vaginal myomectomy.

UAE is now widely used in the US and Western Europe, and has been recommended by the UK's National Institute for Health and Clinical Excellence (NICE) as an alternative therapy to hysterectomy. However, aspects of this treatment are still under evaluation, and complications include premature ovarian failure, chronic vaginal discharge, and in rare cases, pelvic sepsis; UAE may have limited efficacy where the fibroids are large. Although there are a number of reports of successful pregnancy following UAE [7], the experience is limited and research is required in this area. The US Food and Drug Agency (FDA) approved MRgFUS in 2004, while NICE in the UK has recommended that the procedure be used in an audit and research setting [8].

These treatments not only have varying degrees of efficacy, but they all have major cost implications. MRgFUS, for example, requires the availability of costly "open" MR imaging facilities that many units simply do not have, while the costs of the other procedures, including myomectomy and hysterectomy, are well reported in the literature.

It is reasonable to suppose that, given the choice, many women would opt to avoid both the surgical and radiological interventions, as they are invasive, albeit to varying degrees. The ideal alternative would be a relatively cheap tablet taken by mouth, once a day or, better still, once a week, with minimal, if any, side effects, which rapidly induces fibroid regression and a resolution of symptoms with efficacy equivalent or superior to the surgical and radiological treatments, without affecting fertility. At present such a magic bullet medical therapy does not exist, and therein lies the unmet need.

Most of the current medical therapeutic approaches exploit the observations that uterine fibroids have significantly increased concentrations of estrogen (and more recently progesterone) receptors compared with normal myometrium [9, 10], and that ovarian steroids influence fibroid growth. Therefore, most available therapies are hormonal, or act on the relevant hormones or their receptors to interfere with fibroid growth. Thus gonadotropin-releasing hormone (GnRH) agonists (GnRHa) have been used to achieve amenorrhea and shrink fibroid size in symptomatic women, but their use is restricted due to significant side effects such as bone mineral density loss and vasomotor symptoms. They are also notorious for rebound growth of the fibroids upon cessation of therapy. It would be feasible to suggest that there is a very limited role for GnRHa in the management of fibroid disease because they are not cost-effective [11], render myomectomy more difficult because they destroy tissue planes [12, 13], the more difficult enucleation, in fact, increasing rather than reducing perioperative blood loss and operating time. When used prior to myomectomy, they may increase the risk of "recurrence" because they obscure smaller fibroids that "recur" when the effects of the GnRHa wear off [14–16], and are associated with side effects in situations where they confer no benefits, or where alternative cheaper drugs with fewer side effects are available. Selective estrogen receptor modulators (SERMs), such as raloxifene, have been shown to induce fibroid regression in post-, but not premenopausal women. The point here is that medical therapy aiming to antagonize the estrogen effects on fibroid growth has not been a success.

The Emergence of Selective Progesterone Receptor Modulators (SPRMs)

The story of the evolution of SPRMs is a classic example in medicine of a combination of serendipity, the importance of paying attention to clinical observations, and the effective application of translational research. The story started with a woman who had the levonorgestrel-intrauterine system (LNG-IUS) inserted for contraceptive purposes in 1992. On follow-up review the woman, who previously had menorrhagia due to fibroids, reported on the remarkable reduction in the heaviness of her menses, with which she was obviously pleased. This led to a clinical trial of the use of the LNG-IUS for the treatment of women with menorrhagia due to fibroids, and although expulsions of the device were reported in a number of women, they requested re-insertion, and out of the 27 women included none required a hysterectomy, menorrhagia improved, and anemia was corrected [17]. Naturally it was anticipated that the LNG-IUS had

induced involution in myoma volume to cause the reduced menstrual loss, but MR imaging showed that in a third of the women the fibroids had, in fact, increased in size, in another third, they had not changed, whereas in the remaining third they had reduced in size. These unexpected clinical observations led to laboratory in-vitro studies of the impact of progesterone on cultured leiomyoma and normal myometrial cells, and the remarkable findings were that progesterone (P4) acts in combination with estrogen (E2) to stimulate leiomyoma growth and that P4 augments the proliferative activity in cultured leiomyoma cells, but not in cultured normal myometrial cells [18, 19]. These observations raised the tantalizing possibility that molecules that selectively modulate the progesterone receptor could affect leiomyoma cell proliferation without affecting the normal myometrial cell.

Such molecules have been around for some time. For example, ulipristal acetate (UA; Fig. 1) reversibly blocks the progesterone receptor in its target tissues (uterus, cervix, ovaries, and hypothalamus) and acts as a potent, orally active antiprogestational agent, which is why it has been on the clinical scene for some while as an efficient emergency contraceptive.

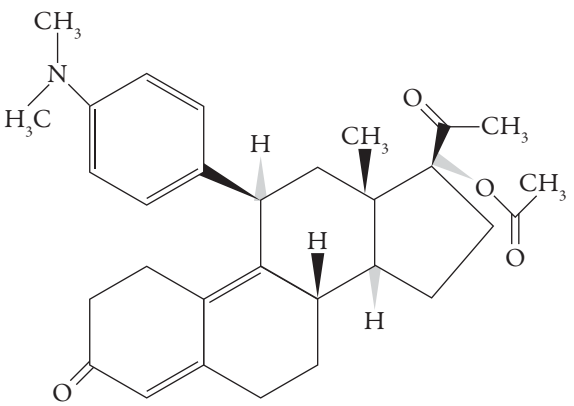

Fig. 1 Chemical structure of ulipristal acetate (17-acetoxy-11ß-[4-*N*,*N*-dimethylaminophenyl]-19-norpregna-4, 9-diene-3,20-dione)

It belongs to a group of compounds collectively known as SPRMs, which include mifepristone, CDB-4124 (telapristone), CP-8947, and J-867 (asoprisnil). A series of laboratory experiments with asoprisnil and UA, as well as the other SPRMs, provided data showing that these compounds act via a variety of mechanisms in-vitro to antagonize the growth of leiomyoma cells but not normal myometrial cells (see below). This then led to the clinical trials that culminated in the emergence of UA as the first-in-class oral SPRM for the treatment of symptomatic fibroids.

UA

Mechanisms of Action of UA

As stated above, through a series of meticulous in-vitro experiments using leiomyoma cells and normal myometrial cells, two important effects were demonstrated. Firstly, it was shown that there is a differential impact of SPRMs on the leiomyoma cells versus the normal myometrium, with no negative impact on the latter. Secondly, it was shown that the SPRMs inhibited leiomyoma cell growth via several mechanisms. The details of the experiments are beyond the scope of this paper, but suffice to summarize:

- UA (and asoprisnil) downregulates the expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and their receptors in cultured fibroid cells [20] resulting in suppression of neovascularization, cell proliferation, and survival [18].
- UA inhibits proliferation of cultured fibroid cells and induces apoptosis by upregulating cleaved caspase 3 and downregulating Bcl-2 [18, 20 21].
- UA increases the expression of matrix metalloproteinases (MMPs) and decreases

the expression of tissue inhibitor of metalloproteinases (TIMPs) and collagens in cultured fibroid cells. This may reduce collagen deposition in the extracellular spaces of fibroids, impairing tissue integrity [18, 20, 22].

- UA modulates the ratio of progesterone receptor isoforms (PR-A and PR-B) in the cultured leiomyoma cells [23] leading to decreased cell viability; suppressed expression of growth factors/angiogenic factors and their receptors in those cells; and induction of apoptosis through activation of the mitochondrial and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathways and endoplasmic reticulum stress [23].

The fact that UA and other SPRMs appear to act via a variety of mechanisms would tend to render them more potent inhibitors of fibroid growth than if they acted via a single mechanism, and this appears to be borne out by the outcomes of clinical trials of UA and other SPRMs.

Evidence for the Effectiveness of UA in the Treatment of Uterine Fibroids

In a number of clinical trials UA has been shown to reduce menstrual loss and fibroid volume and improve quality of life. Unlike GnRHa, UA does not have the side effects of the profound estrogen deficiency and decrease in bone mineral density. In the first trial [24] in which UA was given at 10 or 20 mg in comparison with placebo for three cycles, UA showed a 92% reduction in bleeding versus 19% with placebo. Leiomyoma volume was significantly reduced with UA (29% vs. 6%; $P = 0.01$). UA eliminated menstrual bleeding and inhibited ovulation (percent ovulatory cycles –20% on UA vs. 83% with placebo; $P = 0.001$). UA also improved the concern scores of the uterine leiomyoma symptom quality of life subscale ($P = 0.04$). One woman on UA developed endometrial cystic hyperplasia without evidence of atypia. No serious adverse events were reported. UA did not suppress estradiol and there were no differences in serum estradiol levels between the treatment and placebo groups (median estradiol was greater than 50 pg/mL in all groups). However, the numbers studied were small, with 22 patients being allocated and 18 completing the three cycles or 90–120 day trial [24]. An even more recent randomized, double-blind, placebo-controlled trial of efficacy and tolerability also demonstrated positive results when UA was administered for 3–6 months, showing good control of bleeding, reduction in fibroid size, and improvement in quality of life in the treatment group [25].

UA has recently successfully completed two phase III clinical trials (PEARL I and II) in Europe demonstrating its efficacy and safety for the short-term treatment of symptomatic uterine fibroids in patients eligible for surgery [26, 27]. PEARL I compared treatment with oral UA for up to 13 weeks at a dose of 5 mg/day (96 women) or 10 mg/day (98 women) with placebo (48 women) in patients with fibroids, menorrhagia, and anemia [26]. All patients received iron supplementation. The co-primary efficacy endpoints were control of uterine bleeding and reduction of fibroid volume at week 13, after which patients could undergo surgery. At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5 mg UA, 92% of those receiving 10 mg UA, and 19% of those receiving placebo ($P < 0.001$ for the comparison of each dose of UA with placebo). Treatment with UA for 13 weeks effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids. PEARL II was a double-blind, noninferiority trial that randomly assigned

307 patients with symptomatic fibroids and excessive uterine bleeding to receive 3 months of daily therapy with oral UA (at a dose of either 5 mg or 10 mg) or once-monthly intramuscular injections of the GnRH analog leuprolide acetate (at a dose of 3.75 mg) [27]. The primary outcome was the proportion of patients with controlled bleeding at week 13, with a prespecified noninferiority margin of –20%. Uterine bleeding was controlled in 90% of patients receiving 5 mg UA, in 98% of those receiving 10 mg, while the figure for leuprolide acetate was 89%. There were no significant differences between the UA groups and the leuprolide group in the proportion of patients reporting other adverse events or discontinuing treatment because of adverse events. Both UA doses were noninferior to once monthly leuprolide acetate in controlling uterine bleeding and were significantly less likely to cause hot flashes [27]. The proportions of patients reporting moderate-to-severe hot flashes were 11% in the group receiving 5 mg UA, 10% in the group receiving 10 mg UA and 40% in the group receiving leuprolide acetate ($P < 0.001$ for both comparisons). In fact, the findings suggested that UA could potentially be superior to GnRH analogs for treatment of fibroids due to absence of estrogen suppression and its consequences, a more rapid return of menstruation upon cessation of therapy, and a more persistent shrinkage of fibroids at 6 months posttreatment [27].

Adverse Effects and Concerns Over Long-Term Use of UA

Early clinical studies raised concerns about the effect of SPRMs on the endometrium, and this issue was addressed by a National Institute of Health (NIH) sponsored workshop that evaluated endometrial specimens from women receiving the SPRMs, mifepristone, asoprisnil, and UA [18, 28, 29]. Pathologists concluded that there was little evidence of mitosis consistent with the antiproliferative effect of SPRMs. No biopsy demonstrated atypical hyperplasia. There was asymmetry of stromal and epithelial growth and prominent cystically dilated glands with both admixed estrogen (mitotic) and progestin (secretory) epithelial effects. The panel designated these histological changes as PRM-associated endometrial changes (PAECs) [18, 28, 29]. During 3 months treatment with UA in normal women, no endometrial thickening was observed on ultrasound and examination of the hysterectomy specimens after 3 months of asoprisnil (10 or 25 mg) showed that when compared with placebo, there was a trend for decreased endometrial thickness [18, 30]. In the PEARL II study, endometrial biopsy examinations showed no findings of clinical concern in cases receiving UA. At week 13, all histologic specimens showed benign endometrium except for one patient in the group receiving 5 mg UA, whose specimen showed simple hyperplasia [27]. There were no findings of adenocarcinoma or premalignant lesions. Nonphysiologic endometrial changes were observed in 58% of patients receiving 5 mg UA, 59% of those receiving 10 mg UA, and 12% of those receiving leuprolide acetate. At week 38, after 6 months of treatment-free follow-up, the frequency of nonphysiologic endometrial changes was low and similar in the three study groups (6–7%); all histologic specimens showed benign endometrium, except for one patient (in the leuprolide group) with simple hyperplasia [27].

Based on such findings, it is suggested that unlike in the situation where there is an unopposed estrogen effect, the endometrial thickening in women on PRMs is related to cystic glandular dilation and not endometrial hyperplasia. The overall evidence emerging

from the recent clinical trials regarding the safety of UA, therefore, appears to be reassuring. Clinicians detecting endometrial thickening in women treated with UA need to be aware that administration of UA for longer than 3 months may lead to endometrial thickening. This is related to cystic glandular dilation, not endometrial hyperplasia and pathologists need to be aware of PAECs and avoid misclassifying this appearance as hyperplasia.

However, it is also important to consider the limitations of the current data while describing the effects of UA on the endometrium. Existing studies describe the endometrial changes over short periods (months) of follow-up. Atypical hyperplasia, and possibly malignant change, may take years to develop. Long-term studies are, therefore, necessary to evaluate such outcomes and an appropriate follow-up should be recommended for patients receiving UA until these data are available.

It is also reasonable to suggest that UA may be less effective in the treatment of massive fibroids as it may achieve a modest reduction in their size. Larger clinical trials in future with varying dosages and durations of therapy should provide a definite answer to this question.

Unlike a few other SPRMs, UA has not been reported to cause liver toxicity. There are conflicting reports of its effect on the levels of serum prolactin, and some reports suggest that ovarian cysts may be more common in treated women, but these are thought to arise from abnormal ovulation, are small in size, asymptomatic, and resolve spontaneously [24, 25, 30].

Current Clinical Use of UA and Future Potential

The licensed form of UA is given as a 5 mg once a day oral tablet, taken for 3 months ahead of surgery. Evidence presented above shows that it reduces fibroid volume, reduces menstrual loss or causes amenorrhea, and corrects anemia, and therefore, facilitates surgery. Time will tell if, similar to GnRH analogs, it affects tissue planes at surgery. The current license is too limiting, and further research is required, and indeed, is likely to already be under way, to establish the longer-term safety and efficacy of UA. It would be interesting, for example, to test its effectiveness in the conservative management at the extremes of reproduction: giving it intermittently to the younger woman to control fibroid growth and avoid surgery, and in the older woman, again to control fibroid growth until after the onset of the menopause. As fibroid involution is maintained for prolonged episodes after the resumption of ovulation, the drug could even be used in those women with fibroids just before they try to conceive, but safety and efficacy studies are obviously required.

CONCLUSION

For far too long there has been a pressing need for a medical therapy for the treatment of symptomatic uterine fibroids that is simple, effective, safe, and leads to a resolution of symptoms without affecting fertility. The recent clinical success of UA appears to be a step in the right direction. Given at a 5 or 10 mg daily dose, it is highly effective at reducing menstrual blood loss, affecting amenorrhea in 75% of recipients within 10 days, and has many attributes that arguably render it not only noninferior but potentially superior to GnRH analogs. Researcher-led studies are now required to reproduce these findings, and to evaluate the long-term efficacy and safety, especially with regard to the endometrium, metabolism, and reproductive function. The manufacturers have secured a license for the use of UA in most of Western Europe, including the UK, thus, allowing a variety

of trials to be undertaken to firmly establish the true place of UA in the management of the commonest tumor in women of reproductive age.

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Dr. Manyonda is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

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