Uterine fibroids and Ulipristal

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Abstract

Uterine fibroids, the most common benign gynaecological tumours 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 or radiological but none of these are ideal for every woman. Ulipristal acetate is a selective progesterone receptor modulator which has shown 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 agonists. Presently, it has been licensed in Western Europe for short-term clinical use prior to surgery and further studies are awaited to establish its long-term safety and efficacy.

Keywords fibroids; myoma; selective progesterone receptor modulator; SPRM; Ulipristal acetate

Fibroids are the most common benign tumours in women of reproductive age, with an estimated prevalence of 20–40% of all women by the age of 50. 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. They can cause menorrhagia, dysmenorrhoea and pressure symptoms such as increased urinary frequency, pelvic pain and constipation. Fibroids can also compromise reproduction possibly causing subfertility, miscarriage or complications of pregnancy such as preterm labour, obstructed labour and postpartum haemorrhage.

Contemporary management of uterine fibroids

The current mainstay treatments for symptomatic fibroids are surgical (myomectomy and hysterectomy) and more recently radiological (uterine artery embolisation and focused ultrasound surgery). Although hysterectomy can eradicate all symptoms without possibility of recurrence of the fibroids, it remains unacceptable to many women wishing to retain their uterus.

Myomectomy is a major operation with associated potential morbidity and significant risks of recurrence of the disease or hysterectomy. Uterine artery embolisation (UAE) is being increasingly used to reduce fibroid size but has been associated with a range of complications including premature ovarian failure, chronic vaginal discharge, occasional pelvic sepsis and may have limited efficacy when the fibroids are large. Other treatments such as magnetic resonance imaging (MRI) image guided percutaneous laser ablation and MRI guided transcervical focused ultrasound for fibroids require the availability of expensive MRI facilities that many units do not have and may only be available under research settings.

Traditionally, pharmacological options for treatment of fibroids have been limited. Gonadotropin-releasing hormone (GnRH) agonists have been used to achieve amenorrhoea and reduce fibroid size prior to transcervical resection in symptomatic women, but their use is restricted due to significant side effects such as bone mineral density loss and vasomotor symptoms. They are reasonably expensive, may make myomectomy difficult due to obliteration of tissue planes and are notorious for rebound growth of the fibroids upon cessation of therapy.

Progestrone agents (norethisterone) are commonly used in less resourced settings to induce amenorrhoea while improving anaemia. But side effects include bloating, fluid retention, breast tenderness, weight change, nausea, headache, drowsiness and mood swings. There is no significant reduction in uterine or fibroid volume.

Ulipristal acetate

Ulipristal acetate (UA) is a selective progesterone receptor modulator (SPRM), which was initially licensed as emergency contraception in 2009 and, in May 2012, as a preoperative treatment for fibroids.

UA downregulates the expression of angiogenic growth factors and their receptors in cultured fibroid cells leading to suppression of neovascularisation, cell proliferation and survival. It also increases the expression of matrix metalloproteinases and decreases the expression of tissue inhibitor of metalloproteinases and collagens in fibroid cells impairing tissue integrity. By modulating the ratio of progesterone receptor isoforms, it decreases the cell viability, expression of growth factors and induces apoptosis.

Clinical effectiveness and indication for use of Ulipristal

In a number of clinical trials UA has been shown to reduce menstrual loss as well as fibroid volume and improve quality of life without the side effects of profound estrogen deficiency and decrease in bone mineral density.

In the first trial in which UA was given at 10 mg or 20 mg in comparison against placebo for 3 cycles, UA showed a 92% reduction in bleeding versus 19% with placebo. Leiomyoma volume was significantly reduced with UA (29% versus 6%; P = 0.01). UA also improved the concern scores of the uterine leiomyoma symptom quality of life subscale (P = 0.04). No serious adverse events were reported. Interestingly, 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 3 cycles or 90–120 day trial.

PEARL I was a randomised, parallel group, double blind, placebo controlled phase III trial which compared oral UA for up to 13 weeks at a dose of 5 mg per day (96 women) or 10 mg per day (98 women) with placebo (48 women) in patients with fibroids, menorrhagia and anaemia. All patients received iron supplementation. The co-primary efficacy end points 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 of UA, 92% of those receiving 10 mg of UA, and 19% of those...
receiving placebo ($p < 0.001$ for the comparison of each dose of UA with placebo). Median changes in total fibroid volume were $-21\%$, $-12\%$ and $+3\%$ ($p = 0.002$ UA 5 mg versus placebo, and $p = 0.006$ UA 10 mg versus placebo). The most common side effects were headache and breast pain but there were no significant differences between UA and placebo groups. There was no suppression of estradiol in the women treated with UA in contrast to that seen in women treated with GnRH agonist.

PEARL II was a double blind, non-inferiority, double-dummy phase III trial, which 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 analogue leuprolide acetate (at a dose of 3.75 mg). The primary outcome was the proportion of patients with controlled bleeding at week 13, with a pre-specified non-inferiority margin of $-20\%$. Uterine bleeding was controlled in $90\%$ of patients receiving 5 mg of 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. Both UA doses were non-inferior to once-monthly leuprolide acetate in controlling uterine bleeding and were significantly less likely to cause hot flashes. The proportions of patients reporting moderate-to-severe hot flashes were $11\%$ in the group receiving 5 mg of UA, $10\%$ in the group receiving 10 mg of UA and $40\%$ in the group receiving leuprolide acetate ($p < 0.001$ for both comparisons). These findings suggested that UA could potentially be superior to GnRH analogues for treatment of fibroids due to absence of estrogen suppression and a more persistent shrinkage of fibroids at 6 months post-treatment.

Another double blind, placebo controlled trial of efficacy and tolerability has 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.

Currently UA is prescribed as a 5 mg once a day oral tablet, taken for 3 months ahead of surgery for fibroids. Further studies are required to evaluate the long-term use of UA.

Adverse effects and contraindications

The vast majority of adverse reactions reported with the use of UA are mild, have not lead to its discontinuation and resolved spontaneously. These include hot flushes, headache, functional ovarian cysts, vertigo, nausea, acne, sweating, muscle pain and tiredness.

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. Pathologists concluded that there was little evidence of mitosis and 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).

In the PEARL trials, although non-physiological changes were seen frequently in the UA group, these changes had resolved 6 months after treatment demonstrating reversibility of these changes and safety in this respect of their short-term use.

It has been recommended that UA should be used with caution in those with severe asthma uncontrolled by oral glucocorticoids and those with renal or hepatic dysfunction. Contraindications for UA therapy include pregnancy and breastfeeding, genital bleeding of unknown aetiology or for reasons other than uterine fibroids and uterine, cervical, ovarian or breast cancer.

Summary

With increasing number of women deferring childbearing to their 30s and 40s, when fibroids are most symptomatic, there is a need for a uterus-sparing medical therapy that is cheap, effective and retains reproductive potential. SPRMs hold promise in this area and UA has recently successfully completed Phase III clinical trials demonstrating its efficacy and safety for the treatment of symptomatic uterine fibroids prior to surgery. It has been licensed for short-term preoperative use in Europe. Future research studies are needed to inform the clinicians about its long-term efficacy and safety, especially with regard to the endometrium, other tissues in the body and reproductive function.

Further Reading


