ULIPRISTAL ACETATE – A REVIEW OF THE NEW THERAPEUTIC INDICATIONS AND FUTURE PROSPECTS

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ABSTRACT
Uterine leiomyomata (ULM) are benign smooth muscle neoplasms that are hormone-dependent. Menorrhagia and anemia are the most common symptoms associated with this disorder. As many as 200000 cases of ULM per year are registered in the USA, and hysterectomy remains the major therapeutic option for treatment. Because gonadal hormones induce or maintain leiomyoma growth, selective progesterone receptor modulators have been evaluated as suitable therapeutic agents. Ulipristal acetate (UPA) is a therapeutic agent used as an emergency contraceptive agent. The therapeutic spectrum of the agent has been expanded by a new indication at the end of 2012. Based on two large-scale international randomized trials (PEARL I and PEARL II), UPA (Esmya tab. 5 mg) received European approval for preoperative treatment of ULM in the spring of 2012. The drug is indicated for treatment of moderate to severe symptoms of uterine fibroids. The duration of the treatment with UPA is limited to no more than 3 months when it is used to reduce the size of the tumor, to stop or reduce bleeding and to increase the red blood count prior to surgery. A disadvantage of the cited studies is that the course of treatment is limited to 3 months. Therefore, more data are needed regarding the benefits and risks of long-term treatment with UPA.

The use of UPA in some forms of hypermenorrhoea is discussed as a future therapeutic option but the data are not yet conclusive.

Key words: leiomyoma, ulipristal acetate, progesterone receptors

INTRODUCTION
Uterine leiomyomata (ULM), also called fibromas, are benign, hormone-dependent tumors of the smooth muscle tissue. It has been estimated that 20% to 40% of reproductive age women are affected by them.1,2 The most common symptoms that cannot be adequately controlled with iron preparations are menorrhagia and anemia.5 Other symptoms include pelvic pain, dysmenorrhea and compression, which may adversely affect quality of life and fertility.7-10 The disease is characterized by a high incidence rate. It affects an estimated 24 million women in Europe. In the USA about 200,000 cases are registered annually, and the major treatment modality for the disorder still remains hysterectomy.2

THERAPEUTIC APPROACHES TO ULM
The incidence rate for ULM is typically very high. There are some 24 million women in Europe that are affected by uterine leiomyoma. As many as 200000 cases per year are registered in the USA, and hysterectomy remains the major therapeutic option for treatment.2 Despite the increasing use of organ-sparing surgery, the overall invasive procedure with ULM remains unchanged due to the absence of efficacious conservative alternatives.3 Because sex hormones cause or sustain the growth of ULM4,5, selective progesterone receptor modulators are considered suitable therapeutic agents. Administered for a period of 3-6 months, mifepristone reduces the tumor size and the disease symptoms, inducing amenorrhoea in 63-100% of women.6

Gonadotropin-releasing hormone agonists (GnRH) can be used preoperatively to create an artificial menopause state leading to reversible reduction of the volume of ULM.11,12 These drugs are
also effective in correcting the anemic syndrome.\textsuperscript{13,14} Nevertheless, GnRH agonists are approved only for short-term treatment due to safety concerns (loss of bone mineral density).\textsuperscript{15} Their use is relatively limited also due to adverse reactions, such as hot flashes, depression, mood changes, loss of libido and vaginitis, which occur as a result of estrogen suppression to menopausal levels.

Progestins are frequently associated with breakthrough bleeding which limits their use.\textsuperscript{16} They can induce proliferation of ULM.\textsuperscript{17-19}

A releasing intrauterine system containing levonorgestrel can be used in patients that do not have major deformations associated with ULM or chronic irregular bleeding. Rejection of the intrauterine device is more frequent than that in women with no ULM, and the effect on the volume of ULM is controversial.\textsuperscript{20}

The role progesterone plays in stimulating the ULM growth has generated some interest in creating drugs that modulate its bioavailability. Results from small-scale pilot studies and other uncontrolled studies, in which asoprisnil, mifepristone, telapristone and ulipristal acetate have been used as selective progesterone receptor modulators, indicate the potential benefit of these agents in patients with fibroids.\textsuperscript{21-24}

**MECHANISM OF ACTION**

Ulipristal acetate (UPA) is a selective progesterone receptor modulator (Fig. 1). It produces its effects by a receptor mechanism (progesterone receptors) in the myometrium and endometrial tissue (Fig. 2). As a progesterone receptor agonist, UPA selectively inhibits the proliferation of uterine leiomyoma cells and induces their apoptosis. It modulates the expression of vascular endothelial growth factors (VEGF) and hormone receptors, and modifies the extracellular matrix of the tumor cells, while leaving the myometrium intact. It inhibits ovulation without causing significant changes in serum estradiol levels\textsuperscript{25} or anti-glucocorticoid activity.\textsuperscript{26}

**UPA - DATA FROM CLINICAL TRIALS**

UPA is a drug used as an emergency contraceptive agent. At the end of 2012, a new indication for use was added. It is indicated for treatment of moderate to severe symptoms of uterine fibroids. It is suitable for pre-operative treatment of moderate to severe symptoms of ULM in women of reproductive age. It is used for a maximum of 3 months in order to reduce the size of the tumor, stop or reduce the bleeding and improve the total number of red blood cells prior to surgery.

Levens E et al. reported an improvement in the quality of life of patients in a 3-month administration of the drug. There was no serious adverse reactions (most frequently an antiglucocorticoid effect) over the study period.\textsuperscript{27} Although encouraging, these results need to be further studied comprehensively. Donnez J et al. found that treatment with ulipristal acetate for 13 weeks effectively controlled exces-

**Figure 1.** Chemical structures of selective progesterone receptor modulators. Selective progesterone receptor modulators by N. Chabbert-Buffet et al. Molecular and Cellular Endocrinology 2012;358:232-43.
sive bleeding due to uterine fibroids and reduced the size of the fibroids.28 A therapy with UPA (at a dose of 5 mg or 10 mg) for 13 weeks prior to planned surgery was effective in controlling bleeding, decreasing fibroid volume and reducing discomfort in women with menorrhagia and anemia.28 Similarly, therapy with ulipristal acetate has proved to be effective even in cases of moderate to severe anemia. By applying the new treatment, the quality of life of women is significantly improved, and the incidence of adverse effects leading to discontinuation of therapy is significantly reduced, compared with treatment with GnRH agonists.

Based on two large-scale international randomized studies - PEARL I29 and PEARL II30, in the spring of 2012, UPA (Esmya tab. 5 mg) received European approval for preoperative treatment of ULM to decrease the size of the tumor and control bleeding. In Bulgaria this complementary indication was adopted in September 2012. However, in another recent study published in The Lancet, the patients with preoperative anemia in major non-cardiac interventions showed poorer postoperative outcomes.31 While the gonadotropin-releasing hormone agonists hinder the preparation of the uterine layers for subsequent enucleation of ULM, this does not occur when UPA is used.32 In the first study, 91.5% of women taking Esmya had reduced menstrual bleeding compared with 8.8% of women taking placebo. The size of the fibroid tumors was also smaller in women treated with Esmya than in those who had received placebo. In the second study, Esmya was as effective as leuprorelin in reducing heavy uterine bleeding, with 90.3% of women treated with Esmya showing reduced bleeding compared with 89.1% of those treated with leuprorelin.

ADVERSE DRUG REACTIONS TO UPA

UPA has a specific pharmacodynamic effect on the endometrium (thickening). If this effect persists within 3 months following the end of treatment and return of menstruations, this may need to be monitored to exclude future complications.

The endometrium of UPA treated patients undergoes certain histological changes. They are reversible upon discontinuation of the therapy. These histological changes are referred to as progesterone receptor modulator-associated endometrial changes (PAEC) and should not be confused with endometrial hyperplasia.33

Other common adverse drug reactions according to the definitions used by the European Medicines Agency34, are as follows:

Hot flashes have been reported by 12.7% of women, but the incidence of this adverse drug reaction varies across trials. In the active comparator controlled study the incidence was 24% (10.5% moderate or severe) for ulipristal acetate and 60.4% (39.6% moderate or severe) for leuprorelin-treated
women. In the placebo-controlled study, the incidence of hot flashes is 1.0% for UPA and 0% for placebo.

*Headache* – headaches of mild to moderate severity have been reported by 6.4% of women.

*Ovarian cysts* - functional ovarian cysts have been observed in 1.5% of women during and after treatment, and these, in most of the cases disappeared spontaneously within several weeks.

*Uterine bleeding* - women with heavy menstrual bleeding caused by uterine fibroids are at increased risk of excessive bleeding, which may require surgery. A few cases have been reported during treatment with UPA or within 2 to 3 months after its discontinuation.

*Elevated serum levels of cholesterol and triglycerides*, established by blood tests.

*Others* – vertigo, stomach pain, nausea, acne, increased sweating, muscle and bone pain, tightness (pain) in the chest and/or pain in the lower abdomen (pelvis), uterine bleeding, swelling, fatigue, anxiety, dizziness, epistaxis, xerostomia, constipation, back pain, urinary incontinence, etc.

**CLINICALLY SIGNIFICANT DRUG INTERACTIONS OF UPA**

In using UPA in clinical practice, the following important drug interactions should not be overlooked:

*In vitro* data indicate that UPA can be an inhibitor of the P-glycoprotein (P-gp) at clinically relevant concentrations in the stomach wall and the intestines during resorption. Consequently, concurrent administration of UPA can increase plasma levels of co-administered medicinal products that are substrates of P-gp. Due to lack of clinical data, concurrent administration of UPA and substrates of P-gp (e.g. dabigatran etexilate, digoxin) is not recommended.

As a selective progesterone receptor regulator, UPA can impact the effect of hormonal contraceptive products (progestagen-only contraceptives, progestagen-releasing devices or combined oral contraceptives) and progestagen administered for other reasons. Therefore, concurrent administration of medicinal products containing progestagen is not recommended up to 12 days after treatment discontinuation.

**CONCLUSIONS**

Treatment with UPA for 13 weeks effectively controls excessive bleeding caused by uterine fibroids and reduces the size of ULM.28 A disadvantage of the cited studies is that the course of treatment is limited to 3 months. It has been demonstrated that Esmya improves the symptoms in women with uterine fibroid tumors. More data are needed regarding the benefits and risks of long-term treatment with UPA.

The use of UPA in some forms of hypermenorrhea is discussed as a future therapeutic option but the data are not conclusive.35

**REFERENCES**


ULIPRISTAL ACETATE – НОВАЯ ТЕРАПЕВТИЧЕСКАЯ ИНДИКАЦИЯ И БУДУЩИЕ ПЕРСПЕКТИВЫ – ОБЗОР

Д. Делев

РЕЗЮМЕ

Лейомиома матки (ЛММ) представляет доброкачественную гормонозависимую опухоль гладкой мускулатуры. Самые частые симптомы заболевания это менорагия и анемия. В США регистрируют около 200000 случаев в год, а гистерэктомия остается основной терапевтической опцией лечения. Так как половье гормоны вызывают или поддерживают рост ЛММ, селективные модуляторы прогестероновых рецепторов оценены как подходящие терапевтические агенты. Ulipristal acetate (UPA) представляет медикамент, зарегистрированный как средство для неотложной контрацепции. В конце 2012 г. добавлена новая индикация его применения. На основании двух масштабных международных рандомизированных исследований - PEARL I и PEARL II- весной 2012 г. UPA (Esmya tab. 5mg) получил одобрение применять его для дооперативного лечения ЛММ. Препарат показан при лечении умеренных до тяжелых симптомов маточных фиброзных опухолей. Применяется в течение не более 3 мес. для редукции размера опухоли, прекращения или уменьшения кровотечения и для повышения общего числа красных клеток крови до операции. Недостатком вышеуказанных работ это факт, что терапевтический курс ограничен до 3 мес., и следовательно необходимы побольше данных относительно пользы и рисков продолжительного лечения препаратом UPA.

В качестве будущей терапевтической альтернативы UPA обсуждается его применение при некоторых гиперменорее, но до сих пор имеющиеся данные все еще не категоричны.