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New Drug Update

Role of ulipristal acetate in management of uterine fibroid

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ABSTRACT

Uterine fibroids are most common benign tumors in women of reproductive age group. Prevalence in rural population in India is 37.65% and 24% in urban population. Management depends on number, size, location of fibroid, patients age and fertility preservation. Ulipristal acetate is an orally active synthetic selective progesterone receptor modulator (SPRM). It competes at the progesterone binding site in a tissue specific manner. It decreases fibroid size and relieves symptoms. It inhibits cell proliferation and induces apoptosis leading to shrinkage of tumor. It is indicated for pre-operative treatment and for those who wish to preserve fertility. It is given as four intermittent courses of 5 mg once daily for 3 months. Liver function test has to be done prior to each course. Hence, ulipristal acetate is a promising non-surgical treatment alternative for women with symptomatic uterine fibroids, particularly for those who are not candidates for surgery or who prefer a less invasive approach.

Keywords: Ulipristal acetate, UPA, Uterine fibroid, Medical management, Liver function test, Selective progesterone receptor modulator

INTRODUCTION

Uterine fibroids are most common benign tumors in women of reproductive age group. Prevalence in rural population in India is 37.65% and 24% in urban population. Women may be asymptomatic or significant symptoms can be seen in 25% of women. Women with fibroids may present with abnormal bleeding, infertility, pelvic pain and infertility. Management depends on number, size, location of fibroid, patients age and fertility preservation. It is not infrequent to see women preferring nonsurgical methods for fibroid management to preserve fertility or to postpone surgery. Hence highlighting the significance of medical management.

PATHOPHYSIOLOGY

Previously uterine fibroids were considered estrogen dependent tumors. Lately the role of progesterone and its receptors have been recognized. Progesterone and progesterone receptors (PR) are required for cellular proliferation and fibroid growth. Myoma cells have a higher ratio of estrogen to progesterone receptors as compared to normal myometrial cells. Estrogen binds to its receptor with two times higher affinity and progesterone with three times higher affinity in fibroid as compared to myometrium. Estrogen leads to upregulation of both estrogen and progesterone receptors during follicular phase and during luteal phase, progesterone induces mitogenesis.

Progesterone promotes fibroid growth by upregulating epidermal growth factor (EGF) and B cell lymphoma (BCL-2) gene and by downregulating tumor necrosis factor (TNF) gene. Hence, progesterone and its receptors appear plausible targets to arrest fibroid growth.[1,2]

DRUG

Ulipristal acetate (UPA) is an orally active synthetic selective progesterone receptor modulator (SPRM). It is rapidly absorbed. It acts only on fibroid cells and not on

normal myometrium. It competes at the progesterone binding site in a tissue specific manner. Binding of the SPRM to the PR causes combined agonistic and antagonistic effects which produces partial or mixed effect on progesterone target tissue. It binds to progesterone but not estrogen receptors. It leads to reversible blockage of progesterone receptors. UPA has no affinity towards mineralocorticoide receptor. It decreases leiomyoma size and reduces uterine bleeding in dose dependent manner.[3]

MECHANISM OF ACTION

Molecular mechanism of fibroid regression

It decreases B cell lymphoma (BCL-2) gene expression thereby inhibiting proliferation and induces apoptosis. It downregulates expression of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR), suppressing neovascularization, cell proliferation and survival of the fibroid cell. It increases expression of matrix metalloproteinases (MMPs) and decreases tissue inhibitor of metallo-proteinases (TIMP).

Mechanism of action for relieving fibroid size and symptoms

Action on fibroid cells - it inhibits cell proliferation and induces apoptosis leading to shrinkage of tumor. Action on HPO axis - it inhibits ovulation and induces amenorrhea. It interacts with progesterone receptors of endometrium and induces amenorrhea.[4]

ADVANTAGES

Advantages include symptomatic relief (rapid and reliable bleeding control, especially those nearing menopause), reduction in size of fibroid, prevents surgery (with symptomatic fibroids), prevents recurrence (of fibroid after surgery), retain fertility, and improvement in quality of life.

Table 1: Indications and contraindications.

Indications	Contraindications
Intermittent treatment of moderate to severe symptoms	Pregnancy and breast feeding
Pre-operative treatment	Uterine, ovarian, cervical and breast cancer
	Genital bleeding of unknown origin
	Hypersensitivity to active substance

Candidate

It includes patients with heavy bleeding, those who desire fertility preservation, approaching menopause, patients who want to delay or avoid surgery, for preoperative and postoperative treatment and for recurrent fibroid management.

Dosage

Four intermittent courses of 5 mg once a day for 3 months is given. It is started during first week of menstrual period. Single course treatment is the treatment given for 13 weeks.

Adverse drug reaction

It includes headache and breast tenderness, nausea, abdomen pain (10% of women), and hot flushes (<3%).

Safety concerns

It includes transient increase in endometrial thickness(<10% of women) and progesterone receptor modular changes. No case of endometrial hyperplasia has been reported. Studies have concluded that PAEC does not have any long term implications and disappears after cessation of therapy.

DRUG INDUCED LIVER INJURY (DILI)

Since its authorization in 2012, out of more than 900,000 patients treated with ulipristal acetate for fibroids, five cases of serious liver injury were reported. Among those five, four needed transplants. Therefore, the European Medicines Agency restricted UPA use in February 2018.[5]

The VENUS studies were vital in assessing the effectiveness and safety of UPA in treating symptomatic uterine fibroids (UF). This study showed that it reduces fibroid size along with providing symptom relief with well tolerated safety. UPA was shown to be effective as a preoperative treatment for reducing fibroid size before surgical interventions. VENUS studies confirmed the efficacy of UPA in managing uterine fibroids, particularly in terms of symptom relief and fibroid size reduction.

The PGL 4001 ulipristal acetate efficacy assessment in reduction of symptoms due to uterine leiomyomata (PEARL) studies supported the use of UPA as an effective option for managing uterine fibroids, especially for reducing symptoms and fibroid size. Pearl Study had shown that UPA reduces the size of fibroid, along with reducing symptoms like heavy menstrual bleeding, pelvic pain. Safety profile was favorable with most common side effects like hot flashes, headaches, and nausea. There were also concerns about potential effects on the endometrium, and patients were monitored for changes in the endometrial lining during treatment.[6,7]

NICE guideline (2021) on heavy menstrual bleeding has recommended ulipristal acetate for women with fibroids of 3 cm or more in diameter.

The Medicine and Health Products Regulatory Agency (MHRA) has reinstated the license in February 2021.

Monitoring is required when UPA is used: liver function tests (AST and ALT) prior to starting each treatment course; monthly liver function test during the treatment course; liver function tests 2-4 weeks after completing a treatment course; and signs or symptoms of liver injury should prompt testing.

European Medical Agency's Pharmacovigilance Risk Assessment Committee in May 2018 has recommended the following measures to minimize the risk of the rare but serious liver injury with UPA. It is contraindicated in women with known liver problems. Liver tests have to be done before, during, and after stopping treatment. The use for more than one treatment course has to be restricted to women who are not eligible for surgery.[8]

CONCLUSION

UPA has proven to be an effective treatment option for managing uterine fibroids. UPA offers a promising non-surgical treatment alternative for women with symptomatic uterine fibroids, particularly for those who are not candidates for surgery or who prefer a less invasive approach. It is essential for patients to discuss their individual circumstances and treatment options with their healthcare provider to determine the best course of action for their specific needs.

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