

Effect of Ulipristal Acetate for Uterine Fibroids

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ABSTRACT

BACKGROUND

Fibroids are the most common tumours of the female reproductive tract and have been reported to affect 20-40% of women during their reproductive years. Most fibroids are asymptomatic and require no treatment. We wanted to investigate the effectiveness of Ulipristal Acetate in reducing the fibroid volume, and giving symptomatic relief after 3 months treatment.

METHODS

This is a prospective interventional study conducted among 38 premenopausal women with symptomatic fibroids. They were evaluated clinically for the symptoms reported. Each underwent ultrasound before starting the treatment and after three months of Ulipristal treatment. Some patients had more than one fibroid and so in total the sizes of 56 fibroids were recorded.

RESULTS

After 3 months of ulipristal acetate treatment, patients had a significant improvement of all symptoms with fibroid volume reduction.

CONCLUSIONS

Fibroid treatment with ulipristal acetate resulted in a significant improvement of fibroid related symptoms and significant reduction in fibroid volume.

KEY WORDS

Fibroid, Ulipristal Acetate, Menorrhagia, Selective Progesterone Receptor Modulator, SPRM

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BACKGROUND

Fibroids are the most common tumours of the female reproductive tract and have been reported to affect 20-40% of women during their reproductive years.^[1] Most fibroids are asymptomatic and require no treatment. However the presence of uterine fibroids may lead to serious clinical symptoms such as heavy menstrual bleeding, painful menstruation, pelvic pain, pelvic pressure, urinary frequency or urgency and constipation^[2] The mainstay of treatment of symptomatic uterine fibroids is myomectomy or hysterectomy^[3] but minimally invasive alternatives are also used in clinical practice such as uterine artery embolization^[4] and if the dominant symptom is bleeding hysteroscopic resection of fibroids or endometrial ablation

Management of uterine fibroids: medical treatment's place? No currently available medical treatment is able to eliminate fibroids. Therefore, there is no indication for medical treatment in the absence of symptoms (1) in cases with symptoms f (Pain or Bleeding), the treatment has traditionally been surgical. Based on a large literature review, 4 French recommendations for the management of patients with fibroids concluded that when pregnancy is desired, the hysteroscopic resection of submucosal fibroids less than 4 cm in length is recommended. Interstitial, also known as intramural, fibroids have a negative effect on fertility, but treating them does not improve fertility. Myomectomy is therefore indicated only for symptomatic fibroids, depending on their size and number, and may be performed by laparoscopy or laparotomy. For perimenopausal women who have been informed of the alternatives and the risks, hysterectomy is the most effective treatment for symptomatic fibroids and is associated with a high rate of patient satisfaction.

Because uterine artery embolization is an effective treatment with low long-term morbidity, 4 it is an option for symptomatic fibroids in women who do not want to become Pregnant, and it is a validated alternative to myomectomy and hysterectomy that must be offered to patients. Medical treatment can be used to control symptoms associated with fibroids and can allow surgery to be scheduled under better circumstances (eg, a higher hemoglobin level, or myoma size reduction). Danazol is also often used to control bleeding. However, no randomized controlled trial has proven benefits in the treatment of uterine fibroids. In addition, several side effects have been described, such as acne, hirsutism, weight gain, irritability, musculoskeletal pain, hot flashes, and breast atrophy, all of which limit its long-term use. 12 Oral combined contraceptive pills are often used for young women to control menorrhagia and dysmenorrhea. Unfortunately, such therapy has been very poorly investigated in patients with symptomatic fibroids.

A levonorgestrel intrauterine device can provide a good reduction in menorrhagia, but its effect on the size of uterine fibroids is still being debated. Its use is not recommended in cases with severe distortion of the uterine cavity because of low probability of symptom improvement and the risk of expulsion. Before the arrival of SPRMs, the most efficient medical treatment, as both a conservative treatment and as a preoperative therapy, was GnRH agonists. They induce significant improvements of most symptoms related to fibroids (bleeding, anemia, and pain) and are able to reduce

the volume of fibroids.^[5] However, these effects are transient, and the fibroids usually return to pre-therapy size within a few months of discontinuation.^[6] Furthermore, the chemical castration that GnRH agonists cause leads to menopausal symptoms that limit their long-term use.

Recently, SPRMs have been proved to be efficient in terms of reducing both the symptoms and size of fibroids. 9, 10 the efficacy of these drugs will likely diminish the role of surgery in the management of fibroids. Since progesterone plays a fundamental role in stimulation of myoma growth^[7] modulating it's pathway with selective progesterone receptor modulators such as ulipristal acetate represent one new possibility for medical therapy and ultrasound evaluation of uterine fibroids after ulipristal acetate treatment confirms a reduction in fibroid volume.^[8] It also has advantage of inducing amenorrhea without a negative influence on estradiol levels or anti-glucocorticoid activity.^[9]

The aim of this study was to investigate as to whether after 3 months of treatment with 5 mg of Ulipristal acetate there was any significant change in the fibroid volume and whether patient experienced any relief of symptoms reported earlier at the beginning of the study.

METHODS

This study was designed as a Prospective international study and was conducted from March 2018. Through May 2018 in a single center at Ekopa Hospital, Karad. The sample size of 38 was taken for convenience. Premenopausal women with at least one symptomatic fibroid were included in the study. Patients with previous history of uterine surgery or no suspected cases of adenomyosis or gynaecological malignancy (if required endometrial biopsy done on outpatient basis before including in the study) were excluded from the study. All patients included in the study received 5 mg of ulipristal acetate per day for 3 months continuously. Treatment initiated during first day of menstruation. Informed consent was obtained from all individual participants included in the study. Patients included in the study were scanned by transvaginal ultrasound and evaluated clinically for symptoms reported at least one month before starting the treatment (Baseline) and one month after finishing the three months with ulipristal acetate. Sample size was selected as all the patients who attended outpatient services in the month of March 2018 and were fitting the selection criteria.

Statistical Analysis

Most statistical analyses will be descriptive, reporting subjects counts, means, standard deviations, medians, minima and maxima for continuous variables (e.g. age and duration of symptomatic uterine fibroids) and frequencies and percentages for categorical variables (e.g. disease symptoms, prescription pattern and diagnostic test results). Data regarding symptoms are presented as frequencies and percentages, whereas Ultrasound data are expressed as mean + _standard deviation because of a non-normal distribution. Statistical analyses were conducted with SPSS version 21.0 software. The Student t test was used for comparison between ultrasound features. The Krustal Wallis test was

used to detect differences in fibroid responses to treatment. Correlations were assessed with the Spearman correlation coefficient.

RESULTS

During the period 38 patients were selected who met all the selection criteria. Of the 38 women included in the study 37 completed it and only one patient discontinued before three months due to urticaria reaction. All other patients well tolerated ulipristal acetate in general and only mild side effects were recorded headache (n=8, 21.6%) hot flushes (n=1, 2.7%) and nausea (n=3, 8.1%). The median age was 41 yrs. (Range 32-53) mean 43 yrs.) SD $\pm$ 6 and the median BMI was 24.5 Kg/cm² (Range 19-23 Kg/cm²)

Patients symptoms before and after treatment are shown in Table 1. After 3 months of ulipristal acetate the women had significant improvement of all symptoms reported before the treatment. Main fibroid diameters and volumes before and after 3 months of ulipristal acetate 5 mg treatment are shown in Table. 2 Considering that some patients had more than one fibroid were analysed. The main reduction of fibroids diameters (19%) and volumes (33%) after 3 months of Ulipristal acetate therapy were statistically significant irrespective of location.

Symptom	Before Treatment n (%)	After Treatment
Menorrhagia	26 (68.1%)	4(10.5%)
Pelvic Pressure	21(55.26%)	5(13.15%)
Pelvic Pain	25(65.7%)	2(5.2%)
Urinary frequency	5 (13.15%)	0(0%)

Table 1. Symptoms Reported by the Study Population before Starting the Treatment and 3 Months after Ulipristal Acetate Therapy

The percentages were calculated from the total number of patients (n=38)

Parameter	Before Treatment	After Treatment	Difference
Diameter (mm)	47.20 $\pm$ 18.6	38.4 $\pm$ 14.9	-8.8 $\pm$ 9.6
Volume (cm ³)	61.0 $\pm$ 56.5	10.3 $\pm$ 40.2	-20.7 $\pm$ 27.8

Table 2. Fibroid Diameters, Volumes before and after Ulipristal Therapy and the Differences

p 0.01 for diameter and P 0.01 for volume Data Give As mean $\pm$ SD

DISCUSSION

Selective progesterone receptor modulator (SPRM) are progesterone receptor ligands that display tissue specific interactions with co activators and corepressors leading to mixed agonist and antagonist activity^[10] Although all SPRMS show a similar effect, UPA has shown promising results in terms of efficiency and safety in the treatment of symptomatic uterine fibroids.^{[11],[12]} Progesterone promotes fibroid growth in two ways: 1) it upregulates epidermal growth factor expression and Bcl-2 protein expression; and 2) it down regulates the expression of the tumor necrosis factor gene.¹⁸

SPRMs are a new class of PR ligands that display tissue-selective effects on target cells. UPA is an orally active synthetic SPRM that is characterized by a tissue-specific progesterone antagonist effect. UPA reduces the proliferation of leiomyoma cells and induces apoptosis by increasing the expression of cleaved caspase-3 and decreasing the expression of Bcl-2. Conversely, UPA down regulates the

expression of angiogenic growth factors and their receptors. Thus, it inhibits neovascularization, cell proliferation, and survival in leiomyoma cells, but not in normal myometrial cells. UPA also has a central action on the hypothalamic-pituitary-ovarian axis, and it inhibits or delays ovulation. However, UPA does not change the basic levels of luteinizing hormone or follicle-stimulating hormone, and the estradiol levels remain in the mid-follicular physiological range (60–150 pg/mL). Consequently, UPA does not lead to estrogen deficiency or the symptoms associated with estrogen deficiency. UPA induces amenorrhea in most women because of its interactions with endometrial PRs. However, it is important to keep in mind that UPA should not be given as (or instead of) a contraceptive, although it most likely reduces spontaneous fertility during treatment. The Mechanism of action of ulipristal acetate is its selective antiproliferative and proapoptotic activity and its effect on the pituitary gland and the endometrium.^[13]

Heavy menstrual bleeding is a major cause of doctors' visits of patients with fibroids.^[14] In our study also menorrhagia was the major symptom in all the patients and majority of the patients were relieved of the symptoms. The clinical efficacy and tolerability profile of UPA have been tested in four randomized, double-blind, multi-national, and Phase 3 trials. The first was PEARL I (PGL4001 versus placebo in uterine fibroids), which compared oral UPA (5 or 10 mg/day) to placebo.⁹ The second was PEARL II (PGL4001 versus GnRH analog in uterine fibroids), which compared UPA (5–10 mg/day) with the GnRH analog, leuprolide acetate (LA) (one intramuscular injection per month of 3.75 mg).¹⁰ The third was PEARL III (PGL4001 long-term treatment), where four courses were given over 3 months, with each course of UPA treatment separated by two menstrual cycles.²¹ The final study was PEARL IV, which evaluated the administration of two courses of 3 months of 10 mg/day of UPA. Our results show an overall reduction of fibroid volume by 33% in consistent with findings in literature reporting Fibroid volume reduction between 21.2% and 36%.^[15]

This study had some limitation first of all the study group was small and patients were not blinded to the three-month therapy with ulipristal acetate and these factors may have affected the improvement of symptoms. Ulipristal acetate, a selective P receptor (PR) modulator with pharmacokinetic properties supporting once daily dosing (13) potently modulates PR activity without suppressing E2 to postmenopausal levels and shows proapoptotic / antiproliferative effects on fibroid cells (13–16). Several short-term (3 months) randomized clinical studies showed that ulipristal acetate effectively controls bleeding and shrinks fibroids (13-16) after treatment cessation, return of menstruation usually occurs within 4–5 weeks but fibroid volume reduction can be sustained for up to 6 months. In addition, treatment with ulipristal acetate improved quality of life, reduced fibroid-associated pain, and revealed no safety concerns.

CONCLUSIONS

Ulipristal acetate can be an alternative to hysterectomy for treatment of fibroids. Also, useful where myomectomy is

indicated. If the aim is just improving symptoms, ulipristal acetate is a very good alternative to standard medical treatment in view of its proven effectiveness and safety.^{[8],[16]}

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