Ulipristal Acetate vs. Placebo for Fibroid Treatment Before Surgery

Donnez J Tatarchuk et al
N Eng J med 2012 (Feb); 366(5); 409-20

Fibroid tumors occur in 20-40% of reproductive-aged women and are frequently associated with menorrhagia, anemia, dysmenorrhea and pelvic pain. Fibroid symptoms often adversely affect quality of life and may necessitate medical or surgical intervention. Fibroids are the most common indication for hysterectomy. Myomectomy, hysteroscopic myomectomy uterine artery embolization and other surgical interventions are also available. Treatment choices are generally guided by the age of the patient and their desire for fertility.

Medical therapies have limited utility in the treatment of fibroids. Gonadotropin-releasing hormone (GnRH) agonists may be used pre-surgically, but bothersome symptoms (e.g. hot flashes) and adverse effects on bone mineral density limit their long term use. Progestins and the levonorgestrel-releasing intrauterine device both frequently cause breakthrough bleeding. IUD expulsion is also more common when the uterus is distorted by fibroids.

Research suggests that progesterone promotes the growth of fibroids. Selective progesterone-receptor modulators such as mifepristone and ulipristal acetate have demonstrated some promise in controlling bleeding and reducing fibroid volume. Ulipristal acts on progesterone receptors in myometrium and endometrial, inhibiting ovulation without major effects on estradiol levels.

This randomized double-blind parallel group placebo controlled phase 3 trial was conducted in 38 academic research centers in 6 countries between October, 2008 and August 2010. Women 18 to 50 years old were eligible for inclusion if they had a uterus < 16 weeks size, fibroid 3 - 10 cm in diameter, menorrhagia with a PBAC score of > 100 during menstruation, anemia with a Hb < 10.2g/dl and a BMI between 18 and 40. Participants were randomized in a 2:2:1 ratio to receive a single dose of 10 mg ulipristal daily, a single dose of 5 mg daily, or placebo for up to 13 weeks. All participants received iron supplementation during the study period. After week 13 of treatment, surgery was offered at the discretion of the investigators.

The co-primary endpoints of the study were the percentage of patients with reduction of bleeding at week 13 and the change in uterine volume at week 13. Bleeding was assessed using the PBAC score, a validated instrument in which subjects use standardized sanitary products and a pictorial guide to objectively estimate bleeding. Monthly scores range from 0 (amenorrhea) to over 500. A score of 400 corresponds to blood loss of about 300ml. Efficacy was defined as achievement of a PBAC score < 75 in the 28 days ending at week 13. Uterine volume was assessed by MRI at screening and again at 13 weeks. Secondary endpoints included bleeding pattern, changes in hemoglobin, hematocrit, ferritin, pain and quality of life.

Headache and breast tenderness were the most commonly reported side effects in treated patients, but were not statistically more common than in patients receiving placebo. Endometrial thickness was measured at initial screening and at week 13 by MRI. Reassessment was performed at 26 & 38 weeks in those who had not undergone hysterectomy or endometrial ablation. Endometrial biopsy samples were taken at screening and week 13; with another sample at 38 weeks if no surgical intervention was performed. At baseline and at weeks 5, 9, 13 & 17, serum progesterone, estradiol, prolactin, corticotropin, & thyrotrophin levels were measured.

A total of 462 women were screened, of which 242 were eligible and were randomized. The 230 subjects completing the study included 92 who received 10 mg/day ulipristal, 91 subjects who received 5 mg/day of ulipristal and 47 who received placebo. Menstrual bleeding was effectively controlled (PBAC <75) in 92% of subjects taking 10mg ulipristal, 91% of subjects taking 5mg ulipristal and 19% of those taking placebo. Most patients taking ulipristal became rapidly amenorrhea: 50% of subjects in the 5mg group and 70% in the 10mg ulipristal group achieving amenorrhea within 10 days. The median change in total fibroid volume was -21% in the 5mg ulipristal group, -12% in the 10mg ulipristal group and +3% in the placebo group. The percentage of patients with Hb> 12 g/dl & Hct > 36% increased in all 3 groups as the study
progressed, but Hb & Hct levels were significantly higher in both ulipristal groups at every point in time during the study period. Pain was significantly reduced and quality of life significantly improved among subjects taking ulipristal.

Approximately half of the subjects underwent surgical intervention after the 13 week trial ended. In those retaining their uterus, menstruation resumed an average of 30 days after completion of therapy with between the study groups. Ulipristal induced endometrial thickening at week 13 in a minority of patients. No endometrial hyperplasia or carcinoma was found at biopsy and endometrial thickening had reversed in all subjects who underwent MRI at 26 or 38 weeks.

The current study confirms that short term treatment with ulipristal acetate reduces excessive fibroid related bleeding and fibroid volume, improves hematologic parameters and improves quality of life in women planning fibroid surgery. Reduction in fibroid size may alter the approach. Moreover, ulipristal achieves these effects without suppressing estradiol levels with its associated unpleasant symptoms and adverse effects on bone metabolism. A limitation of this study is its restriction of treatment to 13 weeks. Further study is needed to define the risks and benefits of long-term therapy.