Ulipristal acetate in uterine fibroids

Uterine fibroids (also known as myomas, leiomyomas, or leiomyomatas) represent the most frequent tumor in women of reproductive age (20%–40%) and cause a variety of symptoms that impair a patient's quality of life, including pelvic discomfort, dysmenorrhea, heavy menstrual bleeding with anemia, and reproductive dysfunction. Owing to the limitations of the currently available treatment strategies, which include medical and surgical alternatives, several studies have been conducted in the last few years regarding the use of ulipristal acetate (UPA), a selective P receptor modulator (SPRM) with antiproliferative effects on fibroid cells.

Particularly, two randomized clinical trials—the PGL4001 (UPA) Efficacy Assessment in Reduction of Symptoms due to Uterine Leiomyomata (PEARL) trials I and II—were prospectively conducted (1, 2).

These clinical studies demonstrated that 3 months of UPA administration are efficient for preoperative treatment of symptomatic uterine fibroids. In particular, UPA administration was shown to control excessive bleeding, thereby normalizing anemia; reduce fibroid size and uterine volume for up to 6 months; and decrease pelvic pain, hence restoring quality of life.

The idea to perform intermittent, rather than continuous, treatment courses was developed to address concerns including the safety of SPRMs and potentially adverse endometrial effects.

To date, no long-term intermittent medical treatments for the management of patients with symptomatic myomas have been approved. In this context, GnRH agonists with hormone add-back therapy, oral progestins, and intrauterine levonorgestrel have been used, but all have reported controversial results owing to the regrowth of tumors and the return of symptoms during off-treatment intervals.

The PEARL III and the Extension trial (3) were the first studies in which the long-term efficacy and safety of UPA were evaluated, concretely in four 3-month cycles, separated by a two-month off-treatment period. They showed that 80% of women had a clinically significant reduction in fibroid volume, and the volume of the three largest fibroids was reduced by 72% after four courses of UPA. Moreover, progesterone receptor modulator associated endometrial changes (PAEC), observed in previous studies (1, 2) in approximately 60% of patients, spontaneously reverted within a few weeks to months after stopping UPA therapy. The results of this study (4) also indicated that the incidence of PAEC did not increase after repeated UPA courses. Therefore, intermittent courses of 3-month UPA treatment could be a potential option for long-term medical management of fibroids, since the use of more than one course maximizes the potential benefits of UPA treatment.

Additional long-term effects after UPA therapy have been demonstrated by the publication of the first series of 18 pregnancies (12 resulted in the births of 13 babies, and six in early miscarriages) achieved in 15 infertile women, some of whom did not have surgery after stopping treatment with UPA (4).

In the present issue of *Fertility and Sterility*, Donnez et al. (5) further investigate the efficacy and safety of two repeated 3-month courses of daily UPA 5 and 10 mg for repeated intermittent treatment of symptomatic uterine fibroids (PEARL IV). The authors prospectively observed 451 patients with symptomatic uterine fibroids and heavy bleeding who were randomly allocated to receive either 5 or 10 mg of daily oral UPA during two 3-month courses, separated by an off-treatment period. They showed proportions of amenorrhea in patients who had been treated with 5 and 10 mg UPA of 62% and 73%, respectively, which was higher in the group receiving 10 mg after each treatment course (approximately 83%) than in the group receiving 5 mg (72%–74%). The rate of women with controlled bleeding during the two-treatment course was over 80% even with the 5-mg dose. Menstrual bleeding resumed after each treatment course within a median time $\leq$28 days, and the magnitude of menstruation progressively diminished during the drug-free intervals. Fibroid volume was reduced by 54% and 58% for the 5 and 10 mg UPA patients, respectively. Pelvic pain and quality of life improved in both groups and were partly maintained during the off-treatment period. These outcomes were interpreted with a high level of confidence, given that 90% of patients completed treatment and less than 2% of them interrupted therapy to undergo surgery. Regarding the frequency of PAEC in endometrial biopsies realized after two treatment courses, nonphysiological features were observed in approximately 16% and 19% in the 5 and 10 mg treatment groups, respectively. The authors concluded that 5 or 10 mg daily UPA administered repeatedly during 3-month courses in women with symptomatic fibroids reduces bleeding, discomfort, and fibroid volume, which in turn leads to improvements in quality of life for these patients, without increasing the incidence of PAEC.

In this study, the administration of 5 mg of UPA led to a 38% reduction in fibroids with the first round and a 54.1% reduction with the second, after two menstrual cycles. Thus, compared with previous trials in the same group, this paper shows that providing 5 mg of UPA (which is already the approved dose in Europe and Canada for preoperative treatment) for only two courses significantly reduces fibroids. Furthermore, if surgery is required but there is a wait for some reason, one or two courses of preoperative treatment are sufficient, as no differences are observed between the end of the second round and the first bleeding. That is, the myoma is not affected after a month without treatment.

The present paper also shows us that, with regards to the control of bleeding, the 5-mg dose approved for preoperative use should also be used for long-term symptom management, as it appears to work similarly to the 10-mg dose.

Hence, the results of the current large randomized study provide additional information regarding intermittent treatment, including the reduction of fibroid volume and pain and bleeding control, providing an effective and well-tolerated long-term medical option for fibroids.

Accordingly, this confirms the efficacy and safety of repeated use of UPA in uterine fibroids and provides patients with symptomatic fibroids the option of safely maximizing the efficacy of the therapy for a longer time, while delaying or avoiding recurrence. As in previous clinical studies with the same group, few black patients were included (5.3% and 3.6 in the 5 mg and 10 mg treatment groups, respectively) who are increasingly likely to develop more and more symptomatic fibroids at earlier ages compared to Caucasian women. At the same time, black women and women with fibroids usually present a greater body mass index (BMI) than the patients included in the present trial (BMI of 25.2 and 25.3, in the 5 and 10 mg treatment groups, respectively).

The results of this trial suggest that intermittent UPA, for at least two treatment courses, is an attractive long-term medical option for women with symptomatic fibroids.

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REFERENCES

1. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409–20.
2. Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baro F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366:421–32.
3. Donnez J, Vazquez F, Tomaszewski T, Nouri K, Bouchard P, Fauser BC, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril 2014;101:1565–73.e1–18.
4. Luyckx M, Squifflet JL, Jadoul P, Votino R, Dolmans MM, Donnez J. First series of 18 pregnancies after ulipristal acetate treatment for uterine fibroids. Fertil Steril 2014;102:1404–9.
5. Donnez J, Hudecek R, Donnez O, Matule D, Arhendt HJ, Zatik J, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertil Steril 2015;103:519–27.