Long-term treatment of uterine fibroids with ulipristal acetate☆

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Objective: To investigate the efficacy and safety of ulipristal acetate (UPA) for long-term treatment of symptomatic uterine fibroids.
Design: Repeated intermittent open-label UPA courses, each followed by randomized double-blind norethisterone acetate (NETA) or placebo.
Setting: European clinical gynecology centers.
Patient(s): Two hundred and nine women with symptomatic fibroids including heavy menstrual bleeding.
Intervention(s): Patients received up to four 3-month courses of UPA 10 mg daily, immediately followed by 10-day double-blind treatment with NETA (10 mg daily) or placebo.
Main Outcome Measure(s): Amenorrhea, fibroid volume, endometrial histology.
Result(s): After the first UPA course, amenorrhea occurred in 79% of women, with median onset (from treatment start) of 4 days (interquartile range, 2–6 days). Median fibroid volume change was −45% (interquartile range, −66%; −25%). Amenorrhea rates were 89%, 88%, and 90% for the 131, 119, and 107 women who received treatment courses 2, 3, and 4, respectively. Median times to amenorrhea were 2, 3, and 3 days for treatment courses 2, 3, and 4, respectively. Median fibroid volume changes from baseline were −63%,

Received January 22, 2014; revised and accepted February 6, 2014; published online March 12, 2014.

J.D. has been a member of the Scientific Advisory Board (SAB) of PregLem S.A. since 2007. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. F.V. and his institution received a grant for this study and support for travel to the investigator meetings of the PEARL III and PEARL III extension study. J.T. and his institution received a grant for this study and support for travel to the investigator meetings. K.N. and his institution received a grant for this study and support for travel to the investigator meetings. He was also paid by Gedeon Richter Austria for holding lectures. P.B. is a member of PregLem's SAB. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. B.C.J.M.F. is a member of PregLem's SAB. He received payment for consultancy and was supported for travel to meetings. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. D.H.B. is a member of PregLem's SAB. He received payment for consultancy and data review activities and was supported for travel to meetings. He held PregLem stocks related to SAB activities that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. S.P. and his institution received a grant for this study and support for travel to the investigator meetings. He was also paid by PregLem for his consultancy. O.D. and his institution received a grant for this study. E.B. is an employee of PregLem S.A. She held PregLem stocks related to her employment that she sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug. I.O. and his company Ostermed received payment for consultancy and support for travel to meetings. E.L. is a member of PregLem's SAB. He received payment for consultancy and held PregLem stocks that he sold in October 2010 at PregLem's full acquisition by the Gedeon Richter Group. There is no relationship between stock payment value and future commercial performance of the study drug.
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The clinical trial supporting this work was funded by PregLem S.A., Geneva, Switzerland.
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Fertility and Sterility® Vol. 101, No. 6, June 2014 0015-0282

http://dx.doi.org/10.1016/j.fertnstert.2014.02.008

−67%, and −72% after treatment courses 2, 3, and 4, respectively. All endometrial biopsies showed benign histology without hyperplasia; NETA did not affect fibroid volume or endometrial histology.
Conclusion(s): Repeated 3-month UPA courses effectively control bleeding and shrink fibroids in patients with symptomatic fibroids.
Clinical trial registration: ClinicalTrials.gov (www.clinicaltrials.gov) registration numbers NCT01156857 (PEARL III) and NCT01252069 (PEARL III extension). (Fertil Steril® 2014; 101:1565–73. ©2014 by American Society for Reproductive Medicine.)
Key Words: Long-term treatment, ulipristal acetate, uterine fibroid

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Leiomyomas or fibroids are benign hormone-sensitive tumors of uterine smooth-muscle cells, frequently involving point mutations and/or complex chromosomal rearrangements (1). They occur in about 20%–40% of women of reproductive age (2). Heavy menstrual bleeding (HMB), pelvic pressure and pain, and reproductive dysfunction are common symptoms that impair women's health and quality of life (QoL) (3, 4). Surgical interventions, especially hysterectomy, still predominate the treatment strategy (5). Options for medical therapy are currently limited to preoperative reduction of symptoms related to uterine bleeding and fibroid size; GnRH agonists are licensed but only for short-term therapy owing to safety concerns (loss of bone mass) and adverse reactions (hot flashes) (6, 7). The levonorgestrel-releasing intrauterine device, while not approved for this indication, has been found to reduce menstrual blood loss in women with uterine fibroids, but its efficacy is reduced in patients with a distorted uterus (8). Since February 2012, ulipristal acetate (UPA) is also approved in Europe for preoperative fibroid treatment (9). For the many women wishing to avoid surgery, there remains a substantial need for effective long-term medical therapy.

UPA is a selective P receptor modulator (SPRM) that potently modulates P-receptor activity (10) with proapoptotic/antiproliferative effects on fibroid cells (11) and with pharmacokinetic properties supporting once daily dosing (12). Two short-term (3 months) randomized clinical trials showed that UPA effectively controls HMB and shrinks fibroids (13, 14). After treatment cessation, menstruation usually returns within 4–5 weeks, but fibroid volume reduction can be sustained for up to 6 months. In addition, treatment with UPA reduced fibroid-associated pain, improved QoL, and revealed no safety concerns (13, 14). Clinical trials have also shown that SPRM administration can lead to a pattern of benign, nonphysiological, nonproliferative, histological features of the endometrium termed P receptor modulator associated endometrial changes (PAEC) (15–17). These changes spontaneously reverse over a few weeks to months after cessation of the 3-month UPA treatment (13, 14, 18). Hence, intermittent courses of 3-month UPA treatment with off-treatment intervals are a potential option for the long-term medical management of fibroids (9).

In these two studies, the PGL4001 (UPA) Efficacy Assessment in Reduction of Symptoms due to Uterine Leiomyomata (PEARL) III trial and its extension, we evaluated the sustained effects of UPA on menstrual bleeding, fibroid volume, pain, QoL, and safety during one to four 3-month UPA treatment courses.

Owing to the long-term treatment, no suitable active comparator to UPA was available. However, since UPA exerts mainly antiprogestagenic effects on the endometrium, we randomized women to receive 10 days of treatment with the progestin norethisterone acetate (NETA) or placebo (administered immediately after each completed UPA treatment) to explore any effect on the reversibility of PAEC or timing and magnitude of the next menstruation off treatment. The off-treatment period between each UPA course included one menstrual bleed and the beginning of a second bleed.

MATERIALS AND METHODS

Study Design and Oversight

PEARL III and its extension were long-term, open-label, phase III trials of UPA, which were double-blinded and placebo-controlled toward the administration of progestin after the end of each UPA treatment course. PEARL III was conducted at 21 investigation centers in four countries from July 2010 through November 2011, with 18 centers also participating in the extension protocol until January 2013. The trial and extension were approved by the independent ethics committee of each participating site and were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines.

Study Population

PEARL III enrolled premenopausal women with at least one fibroid ≥ 3 cm in diameter and none >10 cm, HMB, and uterine size <16 weeks of gestation who were eligible for fibroid surgery. Eligible women were aged 18–48 years, with body mass index 18–40 (kg/m^2) and regular menstrual cycles of 22–35 days with FSH ≤ 20 IU/L. Written informed consent was obtained from all women. The main exclusion criteria are listed in Supplemental Table 1, available at www.fertstert.org.

Randomization and Intervention

Women received a 3-month open-label course of UPA (10 mg) once daily immediately followed by double-blind oral NETA (10 mg) once daily or matching placebo for 10 days allocated randomly in a 1:1 ratio.