high rates of resistance that 1 in 5 women initially treated with ciprofloxacin required additional therapy (vs 1 in 4 women initially treated with TMP-SMX. The bottom line is that empiric treatment for postmenopausal women with dysuria requires no urinalysis and should rely on local resistance patterns for the most common urinary pathogens. Women with other UTI symptoms should be evaluated for noninfectious causes while awaiting culture results.—LAL)

Health-related Quality of Life With Ulipristal Acetate for Treatment of Uterine Leiomyomas: A Randomized Controlled Trial

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ABSTRACT

A significant health issue for women in the United States is the occurrence of uterine leiomyomas. The estimated cumulative incidence of uterine leiomyomas by age 50 years is more than 80% in black women and nearly 70% in white women. Up to 50% of the leiomyomas are symptomatic. Abnormal uterine bleeding and urinary frequency are common and have a major negative effect on daily physical and social activities. Other troublesome symptoms include anemia, abdominal pressure and pain, and infertility. Uterine leiomyomas are the leading indication for hysterectomy in the United States. No pharmacologic agents have a Food and Drug Administration–approved indication for treatment of symptomatic uterine leiomyoma other than preoperative therapy.

Ulipristal acetate (UPA), an orally administered selective progesterone receptor modulator (SPRM), has demonstrated efficacy in placebo-controlled trials for treatment of women with symptomatic uterine leiomyomas. Its efficacy was confirmed in 2 pivotal phase 3 studies, VENUS I and VENUS II. In both these trials, rate of and time to amenorrhea were superior for ulipristal 5 or 10 mg compared with placebo ($P < 0.001$).

The aim of this analysis was to provide a more robust and in-depth investigation of the effects of ulipristal on health-related quality of life (QOL) and symptom severity among women with symptomatic uterine leiomyomas and abnormal uterine bleeding in VENUS I and VENUS II. Both VENUS I and VENUS II were phase 3, randomized, multicenter, double-blind, placebo-controlled trials. All women in the 2 trials were randomized to ulipristal (5 and 10 mg) or placebo. At baseline, and over 1 (VENUS I and II) and 2 (VENUS II) 12-week treatment courses, health-related QOL and symptom severity were assessed using the Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire. Data in Venus I and II were pooled. Mean change from baseline to the end of the first course for each Uterine Fibroid Symptom Health-Related Quality of Life scale was analyzed, including a Revised Activities subscale measuring physical and social activities. A change in the Symptom Severity ($\geq 20$ points from baseline) was determined to be a meaningful improvement on the Symptom Severity and Health-Related QOL Total scales was at least a 30-point improvement from baseline on the Revised Activities subscale. For each treatment arm in VENUS II, change from baseline to the end of each course in each scale was analyzed. The intent-to-treat population, including all randomized patients, was the primary population for all analyses.

A total of 589 patients were randomized: 168 to placebo, 215 to ulipristal 5 mg, and 205 to ulipristal 10 mg. Compared with placebo, significantly greater improvements from baseline with both ulipristal doses were found for all Uterine Fibroid Symptom Health-Related Quality of Life scales ($P < 0.001$ for both doses). A meaningful change in Revised Activities was achieved by 34.9% (51 patients) receiving placebo compared with 73.5% (144 patients) receiving ulipristal 5 mg (odds ratio, 5.0; 97.5% confidence interval, 2.9–8.6) and 80.6% (141 patients) receiving ulipristal 10 mg (odds ratio,
At end of courses 1 and 2 in VENUS II, significant improvements from baseline for all Uterine Fibroid Symptom Health-Related Quality of Life scales were found with both ulipristal doses compared with placebo ($P < 0.01$). In VENUS II, beneficial ulipristal effects for Mean Revised Activities scores were maintained in course 2, and improvements were observed after switching from placebo in treatment course 1 to ulipristal in treatment course 2; similar results were found for other scales.

Ulipristal significantly improves health-related QOL and symptom severity compared with placebo in women with symptomatic uterine leiomyomas and is a promising, noninvasive treatment option in this population.

**EDITORIAL COMMENT**

(As noted in the abstract, the VENUS I and II phase 3 trials established that UPA—an SPRM—works better than placebo for control of abnormal uterine bleeding in women with symptomatic uterine leiomyomata. This latest publication focuses on health-related QOL, a useful construct that sums up the impact of UPA's benefits and harms on a patient's physical and psychological well-being. The scale used to assess HRQOL (the UFS-QOL) was developed specifically for women with symptomatic fibroids and has strong validity evidence across multiple studies and populations.

Two 3-month courses of UPA improved HRQOL more than placebo, which is not too surprising but important to quantify. More than one-third in the placebo group experienced a meaningful improvement in HRQOL, and more than twice as many in the UPA groups experienced the same meaningful improvement, with a very small increment of greater improvement after UPA 10 versus 5 mg. It is important to consider that the VENUS trials focused on establishing efficacy evidence and did not include long-term follow-up periods for evaluating safety concerns. Unresolved concerns about endometrial stimulation and potential hepatotoxicity favor a “late adopter” stance for gynecologists who are otherwise enthusiastic about UPA. A systematic review on UPA-induced endometrial changes included only 10 studies comprising 1450 patients with short follow-up periods. The authors called for more safety data prior to concluding that long-term intermittent use of UPA is safe (Eur J Obstet Gynecol Reprod Biol 2017;214:56–64).

Comparative effectiveness trials and long-term observational studies will be needed to clarify the tradeoffs for patients with uterine leiomyomata who are considering hormonal and nonhormonal treatment options for abnormal uterine bleeding. Such trials and economic analyses have already estimated that UPA is less costly than GnRH agonists for preoperative treatment of symptomatic uterine fibroids (J Med Econ 2017;20(3):280–287). Comparing UPA effectiveness and safety to other medical regimens for abnormal uterine bleeding, such as combined hormonal contraceptives and levonorgestrel intrauterine systems, would be a good start, followed by comparative trials comparing UPA to uterus-preservation surgical options such as hysteroscopic and laparoscopic myomectomy.

Along with GnRH antagonists, UPA and other SPRMs are exciting new treatments for patients with abnormal uterine bleeding associated with uterine leiomyomata (Expert Opin Drug Discov 2018;13(2):169–177). Future studies such as the ones noted above will provide greater confidence in their safety and a more accurate appraisal of their effectiveness. For patients who are no longer seeking childbearing or uterine preservation, hysterectomy remains the criterion-standard treatment for fibroid symptoms and HRQOL. Ultimately, long-term cohort studies will be needed to establish the extent to which these new medical alternatives effectively replace versus merely delay hysterectomy.—LAL)