Elagolix Treatment for Up to 12 Months in Women With Heavy Menstrual Bleeding and Uterine Leiomyomas

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ABSTRACT

Uterine leiomyomas affect up to 80% of reproductive-age women and are the most common benign neoplasm of the uterus. A variety of symptoms occur in approximately half of these women; the most common is heavy menstrual bleeding (HMB), which can result in anemia. The mainstay of leiomyoma treatment is surgery; hysterectomy accounts for almost 70% of leiomyoma-related procedures. Symptomatic relief is provided by medical treatment consisting of oral contraceptives, progestins, tranexamic acid, and gonadotropin-releasing hormone (GnRH) agonists, with most providing only short-term efficacy. There is an unmet need as an alternative to surgery for a long-term oral medical treatment that can safely and effectively manage HMB and quality of life for women with symptomatic leiomyomas.

Elagolix, an oral, nonpeptide GnRH antagonist, produces dose-dependent suppression of gonadotropins and ovarian sex hormones and is approved for the management of moderate to severe pain related to endometriosis. Two phase 3 placebo-controlled trials (Elaris UF-1 and UF-2) showed that up to 6 months of elagolix 300 mg twice daily with hormonal add-back therapy (1 mg estradiol and 0.5 mg norethindrone acetate once daily) significantly reduced menstrual bleeding and improved quality of life in women with uterine leiomyomas and HMB.

The aim of this randomized, double-blind, placebo-controlled, phase 3 extension study (Elaris UF-EXTEND) was to investigate the efficacy of elagolix, with hormonal add-back therapy for up to 12 months of treatment in reducing HMB in women with uterine leiomyomas. The study evaluated an additional 6 months (up to 12 months total) of elagolix 300 mg twice daily with hormonal add-back therapy (estradiol 1 mg and norethindrone acetate 0.5 mg once daily) in women who completed an initial 6 months of the same treatment in 1 of 2 preceding randomized, double-blind, placebo-controlled, 6-month phase 3 studies (Elaris UF-1 and UF-2).

Elaris UF-EXTEND was conducted from September 2016 to March 2019 at 115 sites in the United States (including Puerto Rico) and Canada. As in UF-1 and UF-2, the primary study endpoint was the percentage of women with both less than 80 mL menstrual blood loss per cycle during the final month and a 50% or greater reduction in menstrual blood loss from baseline to final month. Women on placebo were randomized 1:1 to receive either elagolix with add-back therapy or elagolix alone for up to 6 months. Follow-up of all women was up to 12 months after treatment. Evaluations of safety included adverse events and changes in bone mineral density. The planned sample size was based on estimated rollover and discontinuation rates in Elaris UF-1 and UF-2.

A total of 433 women were enrolled in Elaris UF-EXTEND between September 2016 and March 2019. Of the 433 women, 218 received up to 12 months of elagolix with add-back therapy. The mean ± SD age of this group was 42.4 ± 5.4 years; 67.3% were Black. Most of the women in the elagolix with add-back group met the primary endpoint (87.9%; 95% confidence interval, 83.4–92.3). With up to 12 months of elagolix plus add-back therapy, the most frequently reported adverse events were hot flush (6.9%), night sweats (3.2%), headache (5.5%), and nausea (4.1%). Decreases in bone mineral density from baseline to extension month 6 were significantly less for elagolix with add-back therapy than with elagolix alone, and differences between groups were statistically significant; the between-group difference in lumbar spine Z score was –3.3, with a 95% confidence interval of –4.1 to –2.5.

These data support the use of elagolix with add-back therapy as a potential new, long-term, oral treatment option for women with uterine leiomyomas and HMB. The data demonstrate that up to 12 months of elagolix with add-back therapy provides...
sustained efficacy in reducing menstrual blood loss and attenuating hypoestrogenic effects associated with the use of elagolix alone. There are no new or unexpected adverse effects associated with an additional 6 months of elagolix with add-back therapy compared with results of the preceding 6-month UF-1 and UF-2 studies.

EDITORIAL COMMENT

(Orally administered GnRH antagonists are emerging as new pharmacologic tools for estrogen-dependent conditions, including pain associated with endometriosis and HMB associated with uterine fibroids. As with GnRH agonists, the antagonists suppress ovarian sex hormones and can create hypoestrogenic adverse effects that limit long-term use. The abstracted study reports the results from the 6-month extension of a phase 3 randomized trial comparing GnRH antagonist treatment alone versus GnRH antagonist plus add-back (daily estradiol 1 mg and norethindrone acetate 0.5 mg) for fibroid-associated HMB. Efficacy (HMB reduction) and adverse effects (bone mineral density and vasomotor symptoms) were compared between groups after up to 12 months of continuous treatment. The imprecise length of follow-up is concerning. The phrase “up to 12 months” was used consistently throughout the article without any information regarding the average or median length of follow-up.

There was a high proportion of data loss comparing the number of patients who joined the extended trial (98 GnRH antagonist alone and 218 GnRH antagonist with add-back), patients who completed an additional 6 months of treatment (79 and 182, respectively), and patients who completed the posttreatment follow-up period of “up to 12 months” (64 and 134, respectively). Comparing initially enrolled patients to the subset who completed follow-up shows large calculated losses in each group (34.7% and 38.5%, respectively). Losses of this magnitude pose a serious threat to validity. Inferences from comparing posttreatment outcomes should be viewed with low confidence because of the high risk of bias.

Before studies conclude that GnRH antagonists reduce HMB because of their impact on uterine fibroids, one must look carefully at their inclusion criteria. The abstracted trial allowed participation of premenopausal women with more than 80 mL of menstrual bleeding per cycle (alkaline hemat estimation), as long as ultrasound-confirmed leiomyomas were present. Baseline leiomyoma volumes had standard deviations much larger than mean values, suggesting that most patients had a low volumetric burden of disease, whereas a few had large, bulky fibroids. With this heterogeneity, it is likely that some participants had HMB caused by fibroids impairing endometrial hemostasis, whereas others had HMB coexisting with more distant intramural and subserosal fibroids. A GnRH antagonist would be expected to improve HMB in either case and also in patients without detectable fibroids. To further establish that these drugs decrease HMB through a biological mechanism involving fibroids, future studies should focus on a more homogeneous clinical group.

Ultimately, understanding the true value of the new GnRH antagonists will require data on their relative effectiveness compared with currently used standard treatments such as hormonal contraceptives and progestins. In addition, trade-offs between symptom control and hypoestrogenic adverse effects will need to be clarified across different dosing regimens (Hum Reprod 2019:34(2):193–199). Establishing the incremental benefit of these new agents for control of both endometriosis-associated pain and fibroid-associated HMB, in comparison with other treatments, will create useful information to guide informed decision making.—LAL)