Gonadotropin-releasing hormone antagonist in uterine adenomyosis: some light at the end of the tunnel

Uterine adenomyosis is described as an estrogen-dependent benign uterine disease characterized by infiltration of the myometrium by endometrial glands to a depth of >2.5 mm. Given its high prevalence and debilitating symptoms, the need for nonsurgical treatment of the disease is becoming ever more pressing, especially for young patients. Current treatment options for adenomyosis are somewhat limited, and many women affected by adenomyosis undergo definitive treatment with hysterectomy. Uterine artery embolization and image-guided endometrial ablation techniques are used to alleviate symptoms in individuals with adenomyosis; however, subsequent pregnancy is not recommended because of substantial risks, including placenta accreta and perinatal mortality. On the other hand, conservative surgery remains a source of contention. Indeed, excisional procedures for adenomyosis run the risk of thinning the uterine walls, thereby creating the threat of uterine rupture during pregnancy.

There is clearly an unmet need for medical therapy for adenomyosis. The main objective of treatment should of course be symptom management; however, the choice depends on both clinical symptoms and patient age and reproductive status. At present, medical treatment options are limited and involve off-label use of hormone therapies or use of analgesics. To date, no drug has been approved for treatment of adenomyosis. Progestogens may be considered an option because they do theoretically have antiproliferative and anti-inflammatory effects; however, progesterone resistance observed in adenomyotic endometrium and stroma curbs their efficacy (1). Relief from pain and bleeding was reported in a long-term study with dienogest but was not confirmed in case of severe adenomyosis.

Oral gonadotropin-releasing hormone (GnRH) antagonists appear to offer a promising new potential treatment alternative, allowing dose-dependent control of estradiol levels with rapid reversibility and no flare-up effect. These drugs are indicated for management of heavy menstrual bleeding (HMB) associated with uterine fibroids or moderate-to-severe pain linked to endometriosis. Some studies suggest that GnRH antagonists may constitute a potential option for treatment of adenomyosis. Indeed, administration of 200 mg of linzagolix daily without add-back therapy has demonstrated the ability of GnRH antagonists to significantly reduce uterine volume (by more than 50%) and manage symptoms in women with severe adenomyosis (2). It should be stressed, however, that quick recurrence of symptoms is typically observed after cessation of therapy. Results from the aforementioned study provided evidence that linzagolix administered at a high dose for 12 weeks, followed by a lower maintenance dose for a further 12 weeks, is a viable alternative for treatment of adenomyosis-related symptoms (2). Unfortunately, the rapid return to baseline values in terms of uterine volume and bleeding indicates that modified regimens are needed for long-term therapy (3).

In Elaris UF-1 and UF-2 clinical trials, 300 mg of elagolix twice daily with add-back therapy (1 mg of estradiol/0.5 mg of norethindrone acetate once a day) significantly curtailed HMB in women with uterine fibroids and concomitant adenomyosis, suggesting that elagolix efficacy was not adversely affected by the presence of adenomyosis (4).

In their article published in the present issue, Catherino et al. (5) report a post hoc analysis evaluating the efficacy of relugolix combination therapy in women with uterine fibroids and concurrent adenomyosis. All of them had completed the pivotal LIBERTY 1 and 2 clinical trials designed to investigate the safety and efficacy of relugolix combination therapy in women with HMB associated with uterine fibroids. In the post hoc analysis, 111 women (18.2% of LIBERTY 1 and 2 completers) met the diagnostic ultrasound criteria for adenomyosis, similar to rates (16%) of coexisting adenomyosis reported in UF-1 and UF-2 trials. This is consistent with the literature reporting concomitant adenomyosis in 15%–57% of hysterectomy specimens with uterine fibroids (4).

In the LIBERTY 1 and 2 post hoc analysis, the subgroup of women with adenomyosis and uterine fibroids was examined against the overall study population on selected efficacy and safety endpoints. Of subjects with adenomyosis, 83.8% in the relugolix combination therapy group responded to treatment compared with 27.6% in the placebo group. Amenorrhea was achieved in 64.9% of women with adenomyosis treated with relugolix combination therapy; however, only 6.9% of those were given the placebo. The least square mean uterine volume of women with adenomyosis decreased by 22.2% and 5.8% in the relugolix combination therapy and placebo groups, respectively. Safety outcomes in the subgroup of women with adenomyosis were comparable with those of the overall LIBERTY 1 and 2 population, with a similar number of adverse events in the relugolix combination therapy and placebo groups. On the whole, efficacy and safety findings in women with uterine fibroids and concurrent adenomyosis were comparable with those in the overall LIBERTY study population. It should be noted that a greater proportion of women in the relugolix combination therapy arm were White (62%), as opposed to the placebo arm (35%). However, in the overall LIBERTY study population, similar outcomes were reported for Black/African American women treated with relugolix combination therapy (5).

As stressed by the investigators themselves (5), limitations of this study include the relatively small number of participants in the analyzed subgroup and lack of stratification upon enrollment according to the presence of adenomyosis. Moreover, being based on retrospective evaluation of ultrasound images rather than magnetic resonance images, disease diagnosis in this study population may be subject to bias.

In women with both uterine fibroids and adenomyosis, relugolix combination therapy yielded similar efficacy to

the overall LIBERTY population, reducing HMB, uterine volume, symptom severity, and pain, and was well tolerated over the course of 24 weeks. This points to no loss of effectiveness in the treatment of fibroids, even in patients with adenomyosis. There is, therefore, a serious need to investigate in future studies the potential medical management of women with both uterine fibroids and adenomyosis.

Nevertheless, data reported in the study by Catherino et al. (5) cannot be extrapolated to women with uterine adenomyosis–related infertility. Randomized controlled trials should certainly be conducted to validate the therapeutic effect of oral GnRH antagonists in women with adenomyosis contingent on the symptoms (bleeding or infertility or both), age, and reproductive status.

CRediT Authorship Contribution Statement

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Declaration of Interests

J.D. has nothing to disclose. M.-M.D. has nothing to disclose.

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