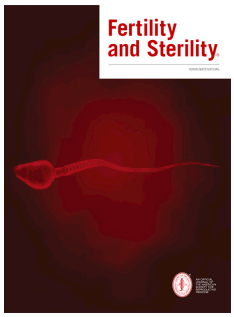

Evolution of uterine adenomyosis volume during and after GnRH antagonist (linzagolix) treatment: lessons for further clinical trials

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Evolution of uterine adenomyosis volume during and after GnRH antagonist (linzagolix) treatment: lessons for further clinical trials

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Keywords: GnRH antagonist, uterine adenomyosis, linzagolix

Objective

Uterine adenomyosis is described as an estrogen-dependent benign uterine disease, characterized by infiltration of the myometrium by endometrial glands to a depth of more than 2.5 mm (**1,2**). Oral gonadotropin-releasing hormone (GnRH) antagonists have been reported to offer a promising new potential treatment option, allowing dose-dependent control of estradiol (E2) levels and characterized by the absence of a flare-up effect and rapid reversibility (**3-5**).

Two previously published papers investigated the impact of linzagolix on uterine volume and symptoms in women with confirmed adenomyosis, evaluating the efficacy of a once-daily dose of 200 mg linzagolix for 12 weeks, followed by a further 12 weeks on 100 mg (**4,5).**

The patients were followed for another 12 weeks without any medication. The objective of the present research letter is to provide updates on uterine volume and other endpoints evaluated 12 weeks after the end of therapy.

Study design

The trial design was approved by the institutional ethics committee and the French National Agency for Drug and Health Product Safety and performed in accordance with International Conference on Harmonization guidelines, all applicable regulations, and the ethical principles of the Declaration of Helsinki. The trial was registered on EudraCT: 2017-004-042-14.
Eight premenopausal women aged 18 to 48 years with a confirmed magnetic resonance imaging (MRI) diagnosis of diffuse adenomyosis **(2)** were given 200 mg/day linzagolix for 12 weeks, before being switched to 100 mg linzagolix for another 12 weeks. After 24 weeks, no further therapy was administered and evaluations were made at week 36. All potential study subjects provided written informed consent.

The primary efficacy endpoint was the change in volume of the adenomyotic uterus from baseline to week 24, evaluated by MRI. Secondary efficacy endpoints included the change in volume of the adenomyotic uterus from baseline to weeks 12 and 36, also by MRI. Other secondary endpoints assessed by MRI were the mean change from baseline to weeks 12, 24 and 36 in the thickest section of the anterior and posterior part of the uterine myometrium

(sagittal assessment), and the largest diameter of the junctional zone (JZ) of the observed adenomyosis. MRI readers were experts in pelvic MRI and blinded to the therapy.

Statistical Analysis

Hypothesis testing was conducted based on change from baseline assessments for reduction in uterine volume by 24 weeks, testing the null hypothesis of no change from baseline versus the alternative hypothesis of a change (increase/decrease) from baseline. Two-sided hypothesis tests were performed at a nominal type I error rate (alpha) of 0.05. Calculated p-values were used primarily as a measure of evidence against the null hypothesis, rather than a formal statement of statistical significance.

The observed change from baseline was described using summary statistics (with appropriate transformations to normalize data as necessary). A formal statistical assessment of change was carried out at each timepoint using repeated-measures methods with two-sided 5% significance levels. The statistical model included weeks (categorical), baseline, and the interaction between weeks and baseline as covariates.

Results

Uterine volume

Mean ± SD uterine volume was 333 ± 250 cm^3 at baseline. By 12 weeks, MRI showed that it had dropped to 159 ± 95 cm^3, yielding a mean reduction of 55% (**Fig 1**). At 24 weeks, uterine volume was 204 ± 126 cm^3 ($p<0.001$), corresponding to a mean decrease of 32% ($p=0.0057$). By 36 weeks, it was 377 ± 298 cm^3, similar to baseline values.

Mean ± SD maximum measurements of the anterior and posterior wall evaluated by MRI were 36 ± 13 mm at baseline and 28 ± 10 mm by 12 weeks, corresponding to a mean decrease of 24%. By 24 weeks, values stood at 31 ± 10 mm, before returning to 35 ± 16 mm by week 36. JZ thickness was 29 ± 12 mm at baseline, 19 ± 12 mm at 12 weeks (mean decrease of 38% from baseline), 23 ± 11 mm at 24 weeks, and 27 ± 18 at 36 weeks. Amenorrhea, defined as no uterine bleeding for at least 35 days, was reported in all women at 12 weeks and 4/7 women at 24 weeks (data on the other woman were missing). Mean time from treatment initiation to start of amenorrhea was 21.3 ± 13.4 days (n=6, median: 22 days, range 4–43 days).

Estradiol levels

Serum E2 was fully suppressed during the first 12 weeks (Fig 2). When patients were switched to 100 mg/day linzagolix, E2 values rose to between 20 and 50 pg/mL. In some individuals, E2 levels occasionally exceeded 100 pg/mL, evidencing the dose-dependent decline in E2 secretion. By week 36 (12 weeks after EOT), E2 levels had returned to values observed in normal ovulatory cycles.

Conclusion

Oral GnRH antagonists have emerged as a potential alternative to allow dose-dependent control of E2 levels (3). During the first 12 weeks of treatment with 200 mg linzagolix, serum E2 levels were rapidly suppressed to below 20 pg/mL. When patients were then given 100 mg/day linzagolix, E2 values increased to between 20 and 40 pg/mL, sometimes climbing above 100 pg/mL. By week 36, E2 levels had returned to values observed in normal ovulatory cycles. The rapid reversibility of oral GnRH antagonist was demonstrated in previous studies (6,7), where resumption of ovarian E2 secretion and ovulation were observed 2-3 weeks after EOT.

Having shrunk by 55% with the higher dose, uterine volume showed a modest increase in size with the lower dose, followed by complete regression to pre-GnRH antagonist therapy levels 12 weeks after EOT. Similar patterns were identified for other secondary endpoints, including the JZ and anterior/posterior wall thickness.

The results of this study provide 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 option for treatment of adenomyosis-related symptoms. Unfortunately, the rapid return to baseline values for uterine volume and bleeding indicates that modified regimens are needed for long-term therapy. An initial course of 200 mg linzagolix for 12 weeks and further treatment with either 100 mg linzagolix or 200 mg linzagolix with add-back therapy should be evaluated for long-term management.

For uterine adenomyosis-related infertility, oocytes can be collected and vitrified before medical therapy with 200 mg linzagolix. After 12 weeks, when efficacy in terms of volume reduction is maximal, therapy can be stopped and embryos transferred 2-3 weeks after EOT. Randomized controlled trials should certainly be conducted to validate this concept.

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Legends to figures

Figure 1: **Uterine volume** in all patients on 200 mg/day linzagolix (week 0-12), and 100 mg/day linzagolix (week 12-24). No therapy was given after week 24. Uterine volume decreased significantly in all subjects taking 200 mg/day linzagolix. Some regrowth was observed with partial E2 suppression on 100 mg/day linzagolix. In all cases but one, uterine volume at 24 weeks remained lower than at baseline. By week 36, it had returned to baseline values.

Fgure 2: **Estradiol values** on 200 mg/day linzagolix (week 0-12), and 100 mg/day linzagolix (week 12-24). No therapy was given after week 24. Serum E2 was fully suppressed during the first 12 weeks. When patients were switched to 100 mg/day linzagolix, E2 values rose to between 20 and 40 pg/mL, occasionally exceeding 100 pg/mL in some individuals. By week 36 (12 weeks after EOT), E2 levels had returned to values observed in normal ovulatory cycles.

Figure 1

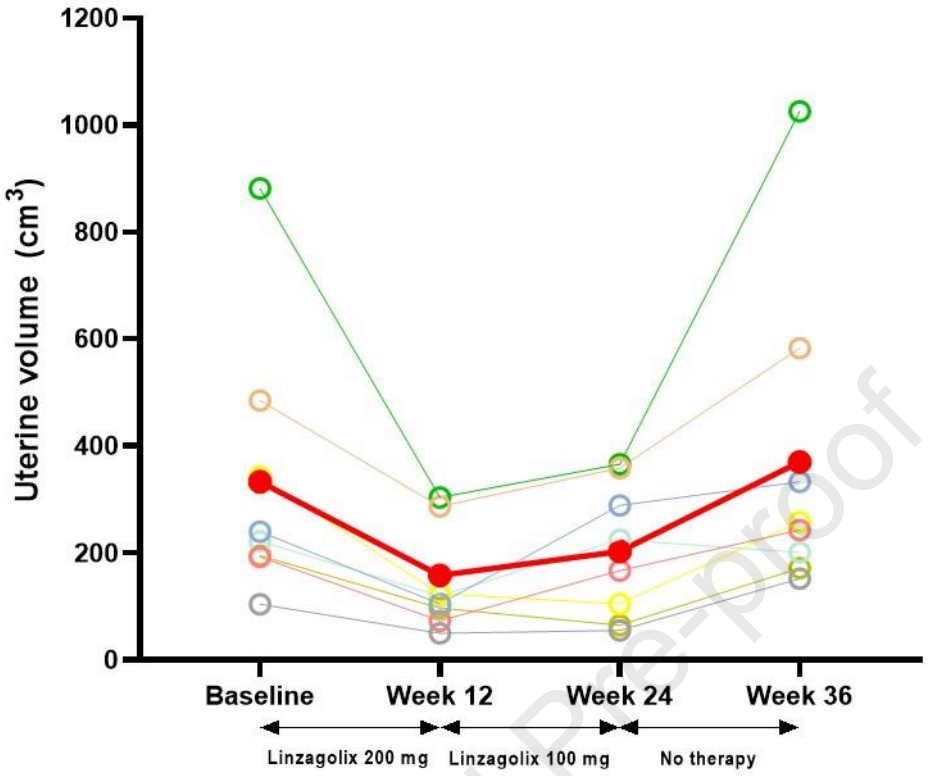

Figure 2