

Spotlight

Combination GnRH antagonists for endometriosis: Balancing efficacy with side effects

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Endometriosis is a chronic pain condition affecting 1 in 10 women. There is an unmet need for better medical treatments for endometriosis. We spotlight trials of a single preparation combined HRT-GnRH antagonist (Relugolix) by Giudice et al.,¹ for endometriosis-associated pain.

Endometriosis is a chronic, neuroinflammatory pain condition that affects 1 in 10 women and those assigned female at birth.² It is characterized by deposits of endometrial-like tissue outside the uterine cavity, most commonly on the pelvic peritoneum and ovaries. It can be associated with a range of painful symptoms, fatigue, urinary/bowel symptoms, and infertility. The impact on quality of life and function is profound.²

Endometriosis-associated pain is managed by analgesics (including neuropathic adjunctive analgesics), surgical removal of endometriosis or drugs that cause ovarian suppression. However, symptoms recur within 5 years following surgery in 40%–50% women,³ existing drug treatments are often ineffective and/or have unpleasant side effects,⁴ and only one-third of patients are satisfied with their current treatment.⁵ GnRH agonists are effective for control of pain⁴ but the profound hypo-estrogenic state induced by their use can result in unacceptable side effects and a reduction in bone mineral density (BMD), limiting their licensed use to the short term only.² GnRH antagonists are similarly effective to GnRH agonists⁶ but, without addback HRT, their use is limited to 24 months, mainly due to their impact on BMD.⁷ There is an unmet need for better treatments for endometriosis.⁸

In the spotlighted SPIRIT 1 and 2 trials, Giudice et al. investigated the efficacy of relugolix 40 mg (an oral GnRH antagonist), in combination with 1 mg estradiol and 0.5 mg norethisterone acetate, for the treatment of endometriosis-associated pain.¹ SPIRIT 1 and 2 were replicate,

phase 3, multicenter, randomized, double-blind, placebo-controlled trials delivered across 219 research centers in six continents. Participants with surgically confirmed endometriosis and moderate (or more severe) dysmenorrhea with associated non-menstrual pain were randomized in a 1:1:1 ratio to either 24 weeks of treatment with relugolix combination, placebo, or to a delayed relugolix arm (12 weeks of relugolix in monotherapy followed by 12 weeks of combination therapy). The use of the “delayed” arm permitted exploration of the impact of hypo-estrogenism on efficacy, tolerability, and BMD. The composite primary outcome in the trial was the proportion of participants achieving a clinically meaningful improvement in dysmenorrhea and non-menstrual pelvic pain (as rated on a 0–10 numerical rating score [NRS]). Secondary outcomes related to other efficacy metrics including the condition-specific quality of life questionnaire, the Endometriosis Health Profile (EHP-30), and safety. In total, 638 and 623 were randomized to SPIRIT 1 and 2, respectively, with similarities in each arm with regard to age, BMI, and ethnicity.

After 24 weeks of treatment, significantly more participants achieved a clinically meaningful improvement in dysmenorrhea NRS (reduction of ≥ -2.8 points) following combination relugolix compared to placebo (SPIRIT 1: 75% versus 27%; SPIRIT 2, 75% versus 30%). Similarly, there was a greater proportion achieving improvement in non-menstrual pelvic pain compared to placebo in both trials (59% versus 40% and 66% versus 43%). Of the key second-

ary outcomes, combination relugolix consistently demonstrated superiority compared to placebo with regard to change in dysmenorrhea, non-menstrual and overall pain (NRS), pain domain score of the EHP-30, and improvement in dyspareunia. At end of treatment those receiving relugolix combination treatment were more likely to be using no analgesia compared to placebo (SPIRIT 1, 56% versus 31%; SPIRIT 2, 54% versus 24%) and a greater number did not require opiates for pain management (SPIRIT I: 86 vs. 76%, SPIRIT II: 82 vs. 66%). Around 75% of participants receiving relugolix combination had either no or infrequent bleeding. Many of the participants in SPIRIT 1 and 2 have entered the “extension arm” of the trial, which allows them to continue treatment for a further 80 weeks. Of those discontinuing relugolix, median return to menses was 31 days, and by 2 months over 90% had menstruated. Adverse event rates were similar between each arm. BMD change after combination relugolix was less than 1% and not deemed to be clinically significant. Those receiving delayed therapy had similar change in efficacy endpoints but were unsurprisingly more likely to experience hot flushes than those with combination therapy and had substantial reduction in BMD after 12 weeks of monotherapy.

These two well-designed, adequately powered trials demonstrate that combination relugolix is effective for moderate-to-severe pain from endometriosis. The delayed combination arm did not have superior efficacy compared to immediate combination therapy, suggesting that



combination therapy is as effective as relugolix without addback HRT, while mitigating impact on BMD and hypo-estrogenic side effects. Combination relugolix has the added benefit of improving compliance with HRT and thus potentially long-term bone health safety. While the results of the extension study are still being awaited, the year 1 data appear encouraging,⁹ and long-term use of combination relugolix may be feasible. As expected, abrogation of menses results in improvement in dysmenorrhea, but critically non-menstrual pain and dyspareunia are also improved. Overall quality of life, as assessed by both the full EHP-30 and the EQ-5D-5L, was not included in the reports. Given that quality of life is one of the key core-outcome set for trials in endometriosis,¹⁰ we hope that the authors will give consideration to publishing these results in the future. Despite the trial's "global approach" to recruitment, over 90% of participants were white, and there is a lack of detail regarding subtype of endometriosis. In the era of precision medicine, determination of the relative efficacy in those with deep, or ovarian, disease compared to superficial peritoneal would have utility. While subgroup analysis on "time since surgical diagnosis" did not affect outcomes, the impact of co-existing peripheral and central sensitization was not assessed. In these patients, symptoms management may require a more nuanced approach, rather than just hormonal suppression, to improve symptoms and quality of life. While the implication of adequate powering to address these and other subgroup analyses is frequently beyond the scope of a single trial, careful phenotyping may permit future network analysis to answer these questions as well as indirect com-

parison to other treatments for endometriosis. Furthermore, direct comparison between combination relugolix and other medical treatment for endometriosis remains to be ascertained.

In conclusion, although additional safety data is required before combination relugolix can be recommended as a long-term treatment for endometriosis, these trials present robust evidence for the use of combination relugolix to treat endometriosis-associated pain while mitigating the deleterious side effects of this class of compounds.

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DECLARATION OF INTERESTS

A.W.H. has received honoraria for consultancy for Ferring, Roche, Nordic Pharma, and Abbvie. L.S. has received an honorarium from Gideon-Richter for attending one advisory board meeting on the use of relugolix combination therapy in the management of fibroids.

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