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The Integral Role of GnRH Antagonists in the Management of Endometriosis

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Al-Hendy:
This is CME on ReachMD, and I'm Dr. Ayman Al-Hendy. Here with me today is Dr. Suzie As-Sanie.

Dr. As-Sanie:
It's a pleasure to be here today, Ayman.

Dr. Al-Hendy:
And Dr. James Simon.

Dr. Simon:
It's a pleasure to be here today, Ayman.

Dr. Al-Hendy:
Let's get into our discussion on the role GnRH antagonists can play in the management of endometriosis.

Suzie, can you please begin by giving us your thoughts on the estrogen threshold hypothesis?

Dr. As-Sanie:
Thank you, Ayman. So let's start by discussing the estrogen threshold hypothesis, which was initially presented by Dr. Barbieri in 1992 and then in more detail in 1998. So there are a lot of gynecologic conditions that we know to be estrogen-dependent diseases that progress and are initiated with the production of estrogen and often regress when estrogen production is reduced. So endometriosis is a classic condition that we know is highly estrogen responsive, and the pelvic pain that's associated with endometriosis often improves when estrogen production is reduced. Unfortunately, though, the reduction of estrogen production is associated with some really significant adverse side effects, such as vasomotor symptoms, such as hot flashes and vaginal dryness, and for a prolonged period of time can lead to irreversible bone mineral density loss. And so the idea of the estrogen threshold hypothesis is, is that we're looking for that sweet spot where the estrogen levels are low enough to cause the regression of estrogen-dependent diseases like endometriosis but are high enough that these adverse side effects, such as vasomotor symptoms and bone mineral density loss, are minimal.

So, Jim, can you please discuss some of the clinical support for the estrogen threshold hypothesis?

Dr. Simon:
Suzie, as you're aware, historically we've done bilateral oophorectomies, significantly reducing estrogen levels, and by doing so, reducing symptoms of endometriosis or really starving the disease of its estrogenic stimulation. That approach unfortunately ends a woman's fertility and provides that beautiful hypoestrogenic environment that's great for endometriosis-related pain, but now she has a

different set of symptoms, those we associate with the hypoestrogenic state, namely symptoms of menopause, hot flashes, night sweats, vaginal dryness, etc., which may or may not be a better set of symptoms than those she had with her endometriosis and its pain. Then we came to having GnRH agonists – agonists. These agents worked first by stimulating estrogen over a short period of time, a few weeks, that actually aggravated endometrioid implants, ruptured ovarian cysts, etc., and then ultimately led to this hypoestrogenic state that we're talking about. We could talk about GnRH agonists as a light switch. If the switch is on, they're not working, and then when they are working, the switch is off. That woman is hormonally menopausal, but caused by a GnRH agonist.

Then came this recent group of GnRH antagonists. As opposed to the switch being on or the switch being off, GnRH antagonists are more like a rheostat. They're dose dependent and therefore can reduce the amount of estrogen in comparable doses. The higher the dose of the antagonist, the greater the suppression of estrogen and the greater the relief of endometriosis-related pain. Further, they don't have any flare effect, that stimulation that I mentioned just a minute ago. And therefore titrating to the desired effect using a GnRH antagonist can provide support for this estrogen hypothesis that Bob Barbieri came up with. That threshold hypothesis suggests that there's a sweet spot between lowering estrogen to reduce the burden of endometriosis disease and its symptoms while still reducing or eliminating or minimizing those menopausal symptoms associated with too great a suppression of estrogen, like we see with the GnRH agonists or high doses of the GnRH antagonists.

Further, that ovarian suppression with either of the agonists or antagonists leads to bone density loss and potential osteoporosis and fractures, which are the long-term concerns of these agents and endometriosis in and of itself.

Ayman, can you speak to some of the specific clinical data supporting GnRH antagonists in the management of endometriosis? And maybe we should get into a discussion of add-back therapy in that setting to mitigate some of these symptoms and long-term bone loss.

Dr. Al-Hendy:
Thank you, Jim, for this overview, and I'll be happy now to go into some of the details of clinical trials that we conducted in the last 3 to 4 years on the role of oral GnRH antagonists in the management and treatment of endometriosis. I'm going to divide this into what we know about relugolix and then end out by giving the data on elagolix. I'm not going to talk a lot about linzagolix because, at the moment, it's not FDA-approved in the United States.

All right, so let's start with relugolix. Relugolix is an oral GnRH antagonist. It is FDA-approved as a combination therapy. So what does that mean? In each one tablet of relugolix there's 40 mg of relugolix, the active ingredient, 1 mg of estradiol, and half a mg of norethindrone acetate, all together in one tablet to be used once a day for treatment of pain associated with endometriosis. There is ample data that we have generated through the clinical research journey of developing and testing relugolix combination therapy against endometriosis. I'm probably going to focus more on the phase 3 trials because these are the direct data that led to the FDA approval.

So the name of that program is called the SPIRIT program. So it started with SPIRIT 1 and 2. These are 6-month phase 3 clinical trials with the highest level of evidence. What I mean by that is randomized, placebo-controlled, double-blind clinical trials. Then that was followed by a 1 1/2 year extension study. So I'm going to talk about that in a couple of minutes. So back to the SPIRIT 1 and 2 clinical trials. These trials, as I said, were 6-month trials. We recruited women with moderate to severe endometriosis. So what does that mean? These are women who scored 4 or above on a specific pain scale called the NRS, numeric rating scale, which is a validated score for pelvic pain. So these women suffered from moderate to severe endometriosis and suffered from moderate to severe pain associated with endometriosis. We recruited up to 800 women in these trials, and they were randomized into 2 arms, either or relugolix combination therapy for 6 months or placebo for 6 months. During that time, we did extensive assessment of efficacy and safety.

Efficacy, we used also validated scores to evaluate their pain, and women who were considered good responders for the treatment had to improve their pain by at least 2.8 points. That means their baseline score has to decrease by 2.8 points at the end of the study to be considered as good responders. It’s a highly stringent endpoint, and that’s both on the menstrual pain, the dysmenorrhea, as well as the noncyclic pelvic pain. Even with this high threshold, about 75% of women on the relugolix combination therapy arm were considered as good responders. This clearly was highly more statistically significant than in the placebo arm. We also saw improvement in other forms of pain, such as dysmenorrhea. We also showed significant decrease in the use of pain medicine, both opioid and non-opioid painkillers.

So these were all very encouraging results. How about the safety side? We looked at different safety outcomes, including side effects. We also particularly wanted to focus on the bone mineral density using DEXA scan. So on the adverse event side, the adverse event profile on the relugolix combination therapy arm was actually not that different from the placebo arm, which is very encouraging. On the bone density scale, there was about 1% decrease in bone mineral density in the relugolix combination therapy arm, but that was generally considered as not clinically relevant.

After that we did, as I mentioned earlier, another extension study for 1 1/2 years, so altogether about 2 years, of patient using relugolix combination therapy. And just to summarize the results of the extension study, at the end of those 2 years, there was no additional

adverse events, so the adverse event signals were very similar to the first 6 months and was favorable, and also there was no further loss of bone mineral density.

Now, I'm going to summarize, quickly, the data on elagolix. Elagolix was evaluated in the program that's called the ELARIS program. So we did a very similar design to what I just described with relugolix. I'm not going to go through that again. It was a 6-month study and then another 6 months extension study.

However, one of the main differences in the elagolix was that elagolix was evaluated alone without additional add-back therapy. It was evaluated as a monotherapy at 2 doses: the low dose, 150 mg once a day, and the high dose, 200 mg twice a day. The efficacy was actually quite favorable and there was significant reduction in pelvic pain associated with endometriosis in the treatment arm compared to the placebo arm. However, unfortunately, the adverse events and the other safety parameters were different. Women on the elagolix-alone arm suffered more hypoestrogenic side effects such as hot flashes, night sweats, etc. There was also significant loss of bone mineral density up to 5% in some patients in the elagolix arm compared to the placebo arm.

Suzie and Jim, I want to thank you very much for being part of this episode.

Dr. Simon:
Ayman and Suzie, it was really great to be part of this program.

Dr. As-Sanie:
It was a pleasure to be here today, Ayman and Jim.

Dr. Al-Hendy:
This discussion has further added to our understanding of the pharmacologic value of oral GnRH antagonists in the management of endometriosis. Unfortunately, our time is up. Thank you, everyone, for listening.

Announcer:
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