Medical management of symptomatic endometriosis: a new weapon in the arsenal?

Until recently, there were few advances over the past two decades in the options available for medical management of symptomatic endometriosis. First-line medical therapies for patients with either documented or clinically suspected endometriosis have typically included the use of continuous combination oral contraceptives, nonsteroidal antiinflammatory drugs, and oral or injectable progestins. Second-line therapy for those who do not respond to this initial approach has included danazol (which has generally been abandoned owing to androgenic side-effects), intrauterine progestins, and GnRH agonists. Although effective in many patients, the latter are associated with hypoestrogenic side-effects, including vasomotor symptoms, vaginal dryness, emotional lability, and bone mineral density loss, that limit duration of use and tolerability. Barbieri had previously proposed an "estrogen threshold hypothesis," suggesting that there might be a window of circulating estrogen levels that can be achieved which is low enough to prevent disease stimulation but high enough to eliminate the side-effects (1). Unfortunately, the specific nature of this window remains undefined and would likely vary among individuals. This concept is also the driving force behind steroidal and nonsteroidal "add-back therapy," which was designed to achieve the goal of providing relief from hypoestrogenic side-effects and maintaining bone mineral density while maintaining the therapeutic efficacy associated with GnRH agonists in this patient population, allowing prolongation of use and increased tolerability (2). Add-back therapy has been met with varying degrees of success depending on the regimen used and does require that the patient take additional medications which can have an impact on compliance.

It appears that we may be ready to begin a new chapter in the treatment of this disease as a host of new medical approaches are being actively evaluated. These include oral GnRH antagonists, selective progesterone receptor modulators, aromatase inhibitors, and peritoneal immune response modulators. The first of these new agents to be approved for use (in the United States, Canada, and Israel to date) is elagolix, an oral GnRH antagonist with a half-life of 4–6 hours. Based on the results of two large prospective, randomized, multicenter, placebo-controlled, industry-funded, 24-week phase 3 trials and extension studies presented in two publications, two separate doses have been approved for use in patients presenting with moderate to severe pain associated with endometriosis: 150 mg daily for up to 24 months and 200 mg twice daily for up to 6 months (3, 4). Dose modification is required for those with severely impaired liver function. Symptoms improved even though amenorrhea was not uniformly achieved nor were E_2 levels uniformly suppressed, which were typically goals of previous therapeutic approaches. However, the lower dose did not effectively treat patients who presented with dyspareunia.

In the current issue of this journal, Donnez et al. present the results of an industry-funded. multicenter. prospective. randomized. placebo-controlled phase 2b dose-ranging study of a second oral GnRH antagonist, linzagolix, in this same patient population with the use of relatively similar end points (5). The half-life of this agent (15–18 h) is longer than that of elagolix, which should allow for once-daily dosing. Four separate individual doses were compared with placebo in a 12-week trial with a 12-week extension in the absence of placebo. After 12 weeks of therapy, the percentages of those who responded to the antagonist regarding overall pelvic pain, dysmenorrhea, nonmenstrual pelvic pain, and quality of life parameters were significantly greater than for those administered placebo for all daily doses $\geq$75 mg. It was not demonstrated whether any of the doses ranging from 75 to 200 mg daily had greater efficacy than any other, because no between-dose comparisons were made. Once again, only the highest dose studied (200 mg daily) resulted in improvement in dyspareunia, which may reflect the presence of more resistant deeply invasive disease. Suppression of E_2 levels, vaginal bleeding, and bone mineral density appeared to be dose related, although that was not formally evaluated. Although the incidence and severity of vasomotor symptoms were not quantified, there also appeared to be a dose-dependent impact. It is encouraging that efficacy was achieved despite that fact that mean circulating E_2 levels were $\geq$20 pg/mL in all but the highest (200 mg) dose. This may suggest a need for add-back therapy in patients treated with this dose.

The investigators should be congratulated for completing a well-designed trial that assessed a host of outcome parameters, including quality of life. The lack of information on the impact of this agent on implants per se reflects an overall shift away from focusing on physical extent of disease and more on effective symptom management, which also avoids the somewhat outdated practice of pre- and post-therapy surgical evaluation.

There are, however, limitations to this investigation which cannot be overlooked. This was not a definitive phase 3 trial, but rather a dose-ranging study, so that ultimate conclusions cannot really be made. Most of the patients were white, and their responses may not reflect responses for other groups. It is also important to note that almost 25% did not complete 24 weeks of therapy. The responses of these dropouts could have a significant impact on analysis of secondary end points. Although there was a decrease in analgesia use across all groups compared with placebo, we must remember that such use was not eliminated, thus implying improvement but not resolution of symptoms. As in the publications regarding elagolix, between-dose comparisons regarding efficacy and side-effects were not performed. We also have no information on clinical outcomes or side-effects with prolonged use beyond 24 weeks, nor is there any information available regarding recurrence rates. In addition, the study was not designed to compare outcomes with those achieved with other established therapeutic agents or surgical intervention. This information would be critical to help inform future treatment strategies.

The results of the trials on oral GnRH antagonists do further support the concept that for most populations of patients with symptomatic endometriosis (with the exception of those presenting with dyspareunia), total E_2 suppression and achievement of amenorrhea is not necessary to achieve symptom relief, which is the underlying principle of the estrogen threshold hypothesis. Based on the results of this trial, it appears that the investigators are considering evaluation of two separate doses of linzagolix in phase 3 studies. The potential of having multiple doses of this agent available is intriguing in that this could allow for individualized dosing regimens addressing specific patient needs and presenting symptoms.

However, one of the concerning implications of incomplete gonadotropin suppression is the conundrum of how to deal with contraception, because pregnancies were reported even in the highly controlled setting of a clinical research trial. One would expect the incidence to be higher if this agent were used in the general population despite appropriate labeling. If contraception is required, which appears to be the case, one must also address the impact that specific methods might have on the efficacy of the antagonist.

So how do we assess the place of linzagolix in our treatment arsenal for women with symptomatic endometriosis? It is a bit too early to say, but it is highly unlikely that this agent, if proven to be effective, would represent a first-line therapy. Its place among second-line or postoperative therapies clearly must wait until we have the results of both the 52-week extension study, a well-designed phase 3 trial, and Food and Drug Administration approval. Cost and efficacy analyses compared with other agents would be critical.

We will need to pay close attention to these developments, but I feel very certain that our options for treating this debilitating disease will be increasing soon!

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