Running title: Relugolix for fibroid-related pain

SHORT-TERM RELUGOLIX TREATMENT FOR FIBROID-RELATED PAIN: WHERE DO WE GO FROM HERE?

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IT'S ALL IN THE DETAILS

Osuga and co-workers report the results of a randomized, double-blind, placebo-controlled trial on the effect of relugolix, 40 mg/day for 12 weeks, in women with pelvic pain associated with uterine fibroids (1). Sixty-five women with a maximum numerical rating scale score of ≥4 during 1 menstrual cycle or other pain symptoms associated with uterine fibroids (e.g., lower abdominal or low back pain) for ≥2 days during 1 menstrual cycle, were recruited. The primary endpoint was the proportion of patients with a maximum score of ≤1 during the 28-day period before the final dose of the study drug. Almost six women out of 10 achieved this outcome (57.6%) in the experimental group versus almost none in the placebo group (3.1%). After 12 weeks of relugolix treatment the median fibroid and uterine volume reduction was 37% and 42%, respectively. More women in the relugolix group experienced untoward effects, especially hot flushes.

Pelvic pain, which is not the most frequent and clinically important symptom associated with uterine fibroids, here had to occur specifically during menstruation. The rapid inhibition of pituitary gonadotropins' release induced by relugolix, leads to anovulation, reduction of serum E2 to postmenopausal levels, amenorrhea and thus, by definition, relief of pain experienced during or exacerbated by menstruations. As placebos generally do not induce amenorrhea, the results of this trial were predictable. Moreover, it may not be excluded that some participants were suffering from undetected endometriosis rather than allegedly symptomatic fibroids.

According to the authors, "blind maintenance was achieved by concealment of the pharmacodynamics test results from all outside parties and personnel involved in the conduct of the study until the randomization code was opened". However, the altered menstrual pattern and the typical vasomotor symptoms associated with relugolix use, renders this measure insufficient to ensure masking of treatment allocation.

The use of analgesics was restricted. Presumably, this favored the experimental group and it would have been interesting to know what would have happened had analgesics be used without restrictions. Only 5.4% of the women allocated to placebo used analgesics in the last month of the

study. This is somewhat unexpected, considering that the main selection criterion was precisely pain

ARE GnRH ANTAGONISTS SUPERIOR TO GnRH AGONISTS?

The present trial demonstrates that relugolix is effective in women with fibroids whose main presenting symptom is pelvic pain. However, behind registration purposes, some authors question the appropriateness of placebo-controlled studies when an effective treatment has already been established (3,4), and women with symptomatic fibroids might be more interested in understanding the added benefits of relugolix over the GnRH agonists they can currently use.

Relugolix was compared with leuprorelin in a non-inferiority trial conducted on patients with fibroid-associated menorrhagia (4). Relugolix was associated with an earlier reduction in the amount of uterine bleeding and a faster recovery of menses after drug discontinuation. All the other outcomes were substantially similar in the two study groups, including the proportion of women achieving amenorrhea, increase in hemoglobin levels, reduction in fibroid and uterine volume, incidence and type of untoward effects, degree of bone mineral density loss, and improvements in health-related quality of life.

Relugolix is clearly a novel drug from a pharmacologic viewpoint, but is the rapidity in the onset and termination of action enough to define this and other GnRH antagonists really novel with respect to GnRH agonists in terms of clinical effectiveness? A faster onset of action can be beneficial in case of severe bleeding, and a faster termination of action is advantageous if intolerable untoward effects arise. In other cases, such differences may result of limited importance.

Much emphasis is being put on avoidance of the flare-up phase when using GnRH antagonists instead of agonists, but the practical impact of this few-day endocrine drawback on the outcome of a treatment enduring months is difficult to quantify. Moreover, the initial pituitary stimulation can be mitigated by injecting leuprorelin during the luteal phase.

According to Mauri and D'Agostino a non-inferiority trial is justified when a new treatment "promise greater safety or convenience, or less expense, while providing similar efficacy". (3) With regard to convenience, i.e., once daily oral versus once monthly intramuscular use, individual preferences seem predominant. Thus, in light of the similar efficacy and safety of GnRH agonists and antagonists, the choice of relugolix would be justified by a lower cost compared with that of leuprorelin. Indeed, a reduction in health care cost could determine the overall value of specific medical interventions (5). Will this be the case?

SHORT-TERM OR LONG-TERM THERAPY?

The mean participants' age in the two study groups was between 40 and 42 years. When considering a medical therapy for symptomatic fibroids in women in their early forties, one crucial issue is to comprehend if this will be a short-term preoperative measure or, alternatively, a long-term treatment aimed at avoiding surgery and reaching the physiologic menopause.

As the final common mechanism of action of GnRH antagonists and agonists is the same, i.e., induced hypoestrogenism, relugolix exerts most likely only temporary effects on fibroid-associated symptoms and lesions' dimension. In this case, fibroid re-growth and symptoms' reappearance are anticipated soon after drug discontinuation. Therefore, once the efficacy of relugolix has been demonstrated in trials of a few-month duration, the obvious question that arises is "what to do next"?

Trials on treatment of women with symptomatic fibroids with relugolix plus add-back therapy for up to 2 years are ongoing. The definitive objective of this type of studies should be to verify whether medical therapy could be considered a clinically effective and cost-effective alternative to surgery. Here the appropriate active comparator is either myomectomy or hysterectomy.

Controlling indefinitely fibroid growth, menorrhagia, and pelvic pain by modulating ovarian steroid production seems an attractive option for many women. However, clinical effectiveness and cost-effectiveness of long-term GnRH antagonist therapy may vary considerably depending on baseline patient conditions and duration of treatment. The balance may be tipped toward medical therapy in patients at high surgical risk and in those who, presumably, are close to menopause. However, in younger women the cost and the potential disadvantages of the medical choice increase in parallel with the expected duration of treatment.

Hysterectomy for symptomatic fibroids is associated with a high degree of patient satisfaction, and morbidity and social costs of surgery are reduced when the procedure is carried out at laparoscopy or vaginally. In premenopausal women, ovarian sparing allows continuation of gonadal function. Moreover, systematic opportunistic salpingectomy might substantially reduce the risk of epithelial ovarian cancer.

"WHAT IS AND WHAT SHOULD NEVER BE" *

*Page J, Plant R. In Led Zeppelin II. Atlantic Records, U.K., 1969

According to Wieseler *et al*. (4) only a limited proportion of new drugs provide real advances over existing ones. Regulators should require evidence from large, superiority, active controlled trials to allow clinical effectiveness comparison and health technology assessment, and inform health care policy. The German Institute for Quality and Efficiency in Health Care categorizes as minor, considerable or major the added benefit of any new drug compared with available drugs, based on importance of the outcome and magnitude of the effect. Reimbursement and pricing decisions should reward achievement of relevant outcomes for patients, disincentivizing marginal ones (4).

Incremental cost-effectiveness ratios (ICER) should be used to weigh trade-offs between health outcomes and costs and identify those medical interventions that improve the health of patients marginally and are not worth the additional costs required (5). This seems important not

only with reference to the final price of relugolix and other GnRH antagonists compared with available GnRH agonists, but also in case of modifications of current indications to medical treatment for fibroids.

For example, in Europe in the past years the indication for ulipristal acetate expanded from a single preoperative course, to multiple courses up to 18 months of treatment as an alternative to surgery. The European Medicine Agency authorized this indication extension without data originating from trials including an active comparator such as a depot GnRH agonist plus add-back therapy or surgery.

Other potential risks associated with the marketing of new drugs for fibroids include broadening of disease definitions (e.g., pelvic pain or sexual dysfunction not necessarily caused by fibroids) and lowering the bar for a medical intervention (e.g., prescribing a medication when surgery would not be required). Moreover, would the frequency of well-women transvaginal sonographies be increased to detect small asymptomatic fibroids to be treated medically before they become so large to necessitate surgery or supposedly jeopardize future fertility (secondary prevention)? Would women who underwent myomectomy be invited to use GnRH antagonists to limit the risk of postoperative recurrence (tertiary prevention)?

Relugolix constitutes an important additional short-term medical option to correct anemia and, when indicated, reduce fibroid and uterine volume before surgery. Ongoing trials will clarify whether long-term use of relugolix plus add-back therapy could be suggested in patients at increased surgical risk. But only comparative effectiveness research and health technology assessment, preferably conducted by independent investigators, might define the number needed to treat and ICER relative to relugolix use in other clinical conditions.

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