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Vercellini *et al.*, 1

1 Running title: Relugolix for fibroid-related pain

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3 **SHORT-TERM RELUGOLIX TREATMENT FOR FIBROID-RELATED**

4 **PAIN: WHERE DO WE GO FROM HERE?**

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## 36 IT'S ALL IN THE DETAILS

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

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

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

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

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

64

#### 65 ARE GnRH ANTAGONISTS SUPERIOR TO GnRH AGONISTS?

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

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

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

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

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

94

## 95   SHORT-TERM OR LONG-TERM THERAPY?

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

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

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

111

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

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

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125 “WHAT IS AND WHAT SHOULD NEVER BE” \*

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

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

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

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

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

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

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

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