Fibroids and medical therapy

Bridging the gap

From SPRM to GnRH antagonist

Uterine fibroids are the most frequent female pelvic tumors and the most frequent indication for hysterectomy, that is associated with morbidity rates of 5% to 8%. Undertaking a myomectomy is also not free of complication and alternative treatments like magnetic resonance guided focused ultrasound and uterine embolization are often proposed (1).

However, there is still a need for medical therapy with the goal to postpone or avoid surgery in women wishing to do so and in women with fibroid-related infertility (1, 2).

Among the available medical therapies, oestro-progestogens (OP) pills and progestogens, although frequently prescribed to women with myoma, are relatively non efficacious at least for women with severe symptoms and large fibroids (2). GnRH agonist are effective in reducing bleeding and fibroid size, but due to menopausal symptoms (hot flushes, vaginal dryness) and Bone Mineral Density (BMD) loss, their use is limited to 3 to 6 months (1, 2).

<u>Selective Progesterone Receptor Modulators (SPRM's): where are we?</u>

In 2012, a RCT demonstrated the advantage of SPRMs (and particularly ulipristal acetate [UPA]) over GnRH agonists (Donnez et al, NEJM, 2012;366:421-32). Indeed, SPRM's reduce the fibroid size and control the heavy menstrual bleeding without inducing hypoestrogenic effects and BMD loss. It was also shown that the progesterone receptor modulator-associated endometrial changes (PAECs) were benign and reversible if intermittent therapy is proposed, allowing the patient to menstruate during the off-period and so, eliminate the endometrial changes induced by SPRM's (1).

Depending on the severity of symptoms, the size and the situation of the myoma, UPA was widely prescribed with the goal to either facilitate surgery or to postpone or avoid surgery (1). A recent review demonstrates the efficacy of UPA in acting on the different mechanisms by which fibroids cause infertility and allowing women to become pregnant without surgery (2). Indeed, the review reported 126 pregnancies in 3 case series and 6 case reports. These reports were retrospective and as such had, of course, some limitations. Nevertheless, we could extrapolate, according to the pathogenic mechanisms, that if a myoma is only slightly distorting the uterine cavity or is intramural and close to the endometrium, it is logical to prescribe UPA with the goal of reducing its size to less than 2.5-3cm and in turn pushing it back into the myometrium (induced migration) and as far as possible from the endometrium (2).

Unfortunately, in 2018, following 5 cases of liver injury (DILI) requiring liver transplantation, the European Medicines Agency (EMA) and its committee of Pharmacovigilance (PRAC) recommended that women should stop taking 5mg UPA (Esmya) while a safety review was ongoing. After the completion of the cases review, the EMA concluded there was a risk of rare but serious liver injury with UPA and in turn new measures, including regular liver monitoring, were implemented to minimize the risk of liver injury in women taking UPA.

The very low incidence of DILI (5 cases among over 900,000 patients who had been treated with UPA since 2012), the existence of comorbidity factors in some cases and the absence of increased liver enzymes in the clinical trials (at the dose of 5mg) lead us to write thet we fear that it was an over-stated tragedy (3).

However, despite the implementation of these new measures to minimize the risks, a new case of serious liver injury occurred in late 2019, which has resulted in the EMA starting other review of the product in 2020.

In total, thus, six cases of UPA-induced liver injury out of over 1,000,000 women treated with UPA have been reported. This incidence is much lower than DILI induced by paracetamol, but these cases neither dose-related nor predictable. The final recommendation and decision of the EMA/PRAC will be taken later this year, and this decision could have far reaching effects on patients who would have previously been treated with UPA.

This in turn could have unfortunate ramifications for us gynecologists and for our patients who have been successfully treated with UPA resulting in the cessation of fibroid-related heavy menstrual bleeding, reduced fibroid volume and subsequent improvement in quality of life.

However, despite the fact we had a highly efficacious drug in our hands, safety should always remain the primary "endpoint" for our patients, and as such as we must accept the final outcome, whatever this may be, from this ongoing review.

Are the oral GnRH antagonists the next step?

Recent Phase 3 results from clinical trials with oral GnRH antagonists (elagolix, relugolix and linzagolix) are very encouraging. The main mode of action, of this class of drug, is the blockage of GnRH receptors resulting in a fast, dose-dependent reduction in estradiol levels, which is quickly reversible.

Since BMD loss was encountered depending on the delivered dose, for the antagonists alone, further phase 3 investigations are underway to assess administration of GnRH antagonist with low-dose hormone add-back therapy (ABT) (1mg estradiol and 0.5mg norethindrone acetate once daily). The goal of this combination is to mitigate the hypoestrogenism-related side effects without decreasing the efficacy benefits.

Some clinical trials like Elaris 1 and 2 are already published (4). Results of others are accessible. This is the case for Liberty 1 and 2 and Primerose 2 (see reference2).

During the Elaris 1 and 2 trials, performed in sites within the United States of America (US), 300mg elagolix was administered twice a day (elagolix plus add back in the morning, followed by elagolix alone in the evening) (4). The primary endpoint was a reduction of menstrual blood loss to less than 80ml and at least a 50% reduction in menstrual bleeding from baseline to the final month, after 24 weeks of treatment. The percentages of women who met these criteria for the primary endpoint were 68.5% and 76% respectively for Elaris 1 and 2 (Figure 1). The fibroid volume reduction evaluated by MRI was approximatively 10%. With respect to the change in bone mineral density, there was a greater decrease in women treated with Elagolix + ABT for 6 months (-0.7%) compared to placebo (-0.1%)

In two other recently completed clinical trials (Liberty 1 and Liberty 2 [see reference 2]), women, in both US and Non-US sites, received 40 mg relugolix with corresponding add-back therapy (relugolix combination therapy), combined in one pill, once per day. The percentages of women who met the primary endpoint (menstrual blood loss <80 ml and >50% reduction from baseline after 24 weeks of treatment) were 73.4% and 71.3% respectively in Liberty 1 and Liberty 2 (Figure 1). Amenorrhea rates were 52.3% and 50.4% respectively and spine BMD loss -0.36% and -0.13. During these trials the change in bone mineral density of the relugolix combination therapy, was not significantly different compared to women who received placebo.

The third oral GnRH antagonist currently undergoing phase 3 clinical trials is linzagolix. In the first randomized clinical trial (Primrose 2 [see reference 2]), in both US and Non-US sites, (Figure 1), the proportion of women who met the primary endpoint (the same as in elagolix and relugolix trials) was 93.9% at a dose of 200 mg Linzagolix plus add-back therapy (Once per day). The time required to reduce menstrual blood loss was very fast in the 200 mg Linzagolix + ABT group, with 70% of women meeting the primary criteria after one week. The

percentages of women in amenorrhea at 24 weeks was 80.6% and fibroid volume change from baseline was -29.4% in the 200 mg Linzagolix + ABT groups. BMD loss was evaluated at -1.31% in the spine.

In conclusion, results from the phase 3 clinical trials with three different oral GnRH antagonists (elagolix, relugolix, linzagolix) have demonstrated excellent control of fibroid-related heavy menstrual bleeding and proved that the reduction in menstrual bleeding is maintained when add-back therapy is taken with the antagonists, whilst at the same time maintaining the loss of BMD to a level equivalent to Placebo.

During the PRIMROSE 2 RCT, the reduction in fibroid volume was, however, more limited in the group with ABT compared to the group without ABT. As suggested in a recent paper (5), it could be more appropriate if myoma size reduction is the main goal of the treatment, to start with a therapy of GnRH antagonist (alone) to induce a quick hypoestrogenism with a subsequent fast response in terms of volume reduction, as we have already shown in severe adenomyosis cases and then follow with a combination therapy approach for long term treatment (5). It could indeed be hypothesized that the progestogens given in the ABT group reduced the efficacy of the GnRH antagonist in myoma size reduction as it is well known that progesterone and progestogens are responsible for myoma growth.

We have the exciting situation to have in our hands new drugs for the treatment of the symptoms associated with UF, and as such there is an urgent need to develop new algorithms according to the severity of symptoms, the location of the myoma according to the FIGO classification, the age of the women and her desire to avoid or postpone surgery and preserve fertility and uterus (1, 2) and to evaluate the place of medical therapy as a primary approach to treat our patients.

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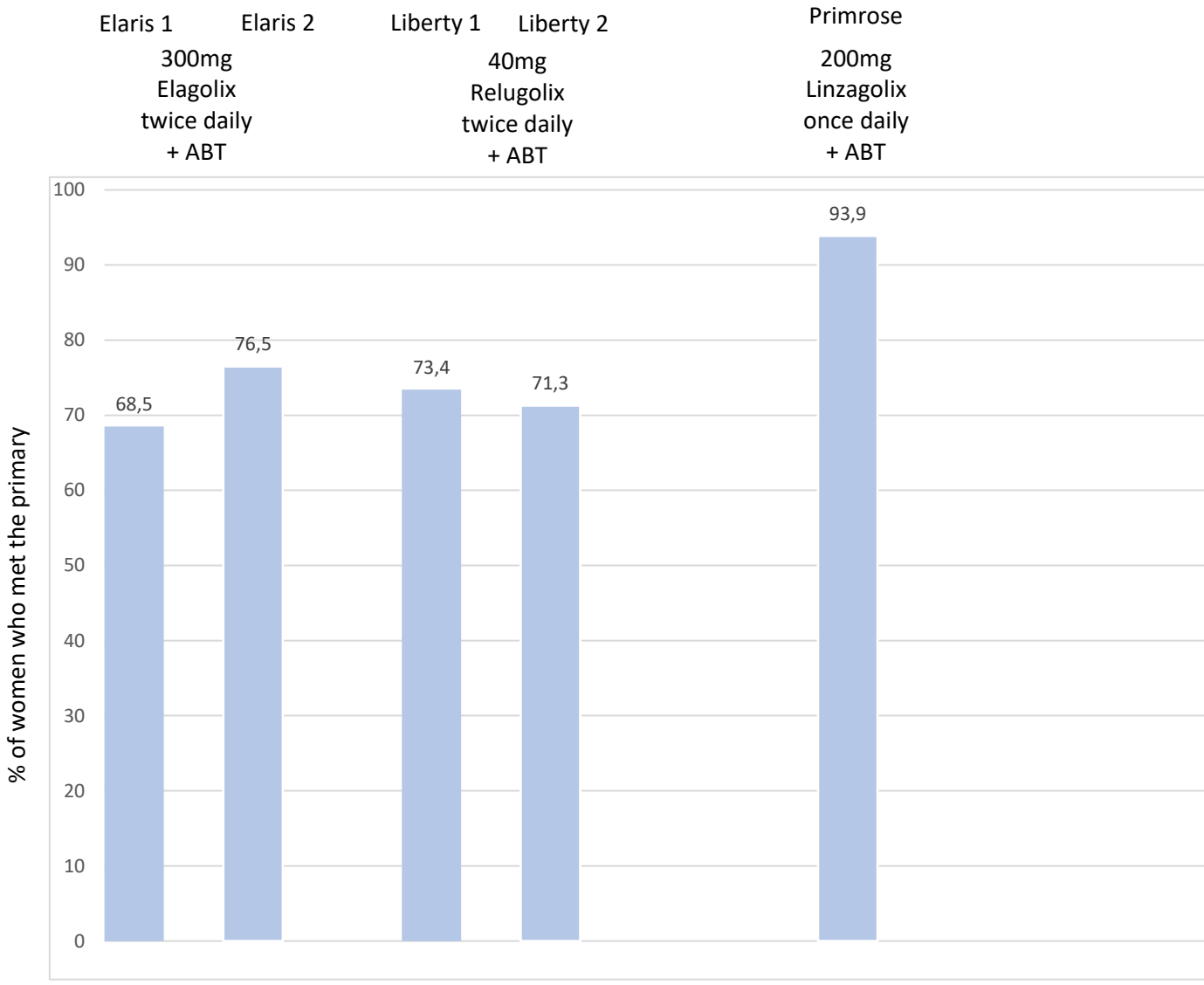
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References:

1) Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016;22:665-686.
2) Donnez J, Dolmans MM. Intramural myoma-related infertility: the place of hormone therapy in infertility management: from UPA to GnRH antagonist. A review. RBMonline. 2020 (https://doi.org/10.1016/j.rbmo.2020.05.017 1472-6483).
3) Donnez J. Liver Injury and Ulipristal Acetate: An Overstated Tragedy? Fertil Steril. 2018;110:593-595.
4) Schlaff WD, Ackerman RT, Al-Hendy A, Archer DF, Barnhart KT, Bradley LD, Carr BR, Feinberg EC, Hurtado SM, Kim J, Liu R, Mabey RG Jr, Owens CD, Poindexter A, Puscheck EE, Rodriguez-Ginorio H, Simon JA, Soliman AM, Stewart EA, Watts NB, Muneyyirci-Delale O. Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids. N Engl J Med. 2020;382:328-340.
5) Donnez O, Donnez J. Gonadotropin-releasing hormone antagonist (linzagolix): a new therapy for uterine adenomyosis. Fertil Steril. 2020:S0015-0282(20)30345-9.

Figure:


Elaris 1
Elaris 2
Liberty 1
Liberty 2
Primrose
300mg Elagolix twice daily + ABT
40mg Relugolix twice daily + ABT
200mg Linzagolix once daily + ABT
% of women who met the primary
100
90
80
70
60
50
40
30
20
10
0
68,5
76,5
73,4
71,3
93,9

Legend to figure:

Percentage of women who met the primary endpoint (proportion of women with menstrual blood loss <80ml and ≥50% from baseline in 3 clinical trials with oral GnRH antagonist (elagolix + ABT; relugolix + ABT, linzagolix + ABT).