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POSITION STATEMENT

It's time to make a change from a lesion-tailored to a patient-tailored approach in the management of uterine fibroids

Short title: *New medical approach for treatment of uterine fibroids*

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ABSTRACT

The management of patients with uterine fibroids (UF) has changed substantially during the last century thanks to the development of new drugs focused on symptom management.

The burden of UF on women's lives is significant for the severity of the symptoms (mainly heavy menstrual bleeding, pain, bulk symptoms and even impaired fertility) that can negatively affect their quality of life from a personal, familiar and professional point of view. The current approach should take into account all women's needs, their daily problems and their fears and expectations, shifting from a lesion-oriented vision to a patient-oriented one.

The new tools for the medical management of UF currently available, the oral GnRH antagonists with add-back therapy (ABT), allow great flexibility with safe options.

Relugolix Combination Therapy (40mg Relugolix + 1mg oestradiol hemihydrate + 0.5mg norethisterone acetate), one tablet daily, is licensed for the treatment of moderate to severe symptoms of UF in adult women of reproductive age. The triple combination has the aim of combining preventive activity on the growth of UF with the maintenance of oestradiol and progesterone levels in an optimal therapeutic range, in order to minimize the adverse effects. In the phase 3 double-blind trials, Relugolix CT producing oestradiol concentrations of 33 pg/ml, as in the early follicular phase within the therapeutic window, represents a balanced long-term treatment.

In a new holistic, patient-oriented approach, the ability of Relugolix CT to improve the most common and troublesome symptoms associated with UF and related distress, has significant clinical and socio-economic implications.

Key words

Uterine fibroids; medical therapy; drug combination; GnRH antagonists; relugolix.

Introduction

The choice of therapeutical approaches for uterine fibroids (UF) varies on the basis of several factors, and therefore should be applied individually. The first laparotomy consequent to myoma indication was performed in 1809 by Ephraim McDowell on a cousin of President Abraham Lincoln[1] and hysterectomy became the standard of care in the management of uterine myomas for a long time.

The management of patients with UF has changed substantially during the last century also thanks to the development of new drugs focused on symptom management, enriching the doctor's bag and making the role of medical treatment increasingly important. The historical approach with gonadotropin-releasing hormone analogues (GnRHa) showed efficacy in controlling symptoms and reducing myoma size, but their use has been associated with significant short- and long-term side effects, such as the initial flare-up effect, the rebound effect that appears with treatment discontinuation, but mainly postmenopausal symptoms and osteoporosis [2, 3]. In July 2012, the availability in Europe of Ulipristal acetate (UPA), a selective modulator of progesterone receptor, changed forever the paradigm of surgery as the only therapeutical option. However, in July 2018, a safety review after rare cases of severe liver damage were reported, restricted indications of UPA as only a second line option for women of reproductive age when surgery/embolization failed or was impracticable [4].

It has to be remembered that uterine sarcomas are rare uterine neoplasms, often diagnosed after hysterectomy or myomectomy for assumed leiomyomas [5]. When there is concern that the leiomyoma may be a sarcoma, both endometrial biopsy and MRI appear to be useful in differentiating diagnosis [6].

Women's unmet needs

The burden of UF on women's lives is significant for the severity of the symptoms referred, that can negatively affect the quality of life of the patients, also from a personal, familiar and professional point of view [7–9] (Table 1). One in four women with UF are symptomatic, with many women exhibiting more than one symptom [10]; UF may cause bleeding, in particular heavy menstrual bleeding (HMB) and anaemia. Moreover, UF may be responsible for chronic pain or pain during the menstrual cycle, in the pre-menstrual or post-menstrual period, during ovulation, during sexual intercourse, as well as bulk symptoms, depending on their size and location, such as abdominal protrusion, incontinence, urinary urgency, pelvic pressure, constipation, tenesmus, and even impaired fertility [7, 11, 12] Many women report fatigue, missing work hours and loss of productivity because of UF [8, 9]. Symptomatic UF may lead to depression, increased anxiety (about bleeding, pain, unpredictability of symptoms, development into cancer), social isolation, feelings of helplessness, and negative body image and sexuality [8, 13–15].

Previous studies have suggested that successful treatments for UF are associated with reductions of approximately 20–30 points in symptom severity scores and 20–40-point increases in HRQoL scores [2, 16–18]. It can be argued that the problem is not always the benign lesion itself, but the symptom burden that women suffer.

Already in 2017, the Italian Society of Gynaecology and Obstetrics (SIGO) stated in its Guidelines for diagnosis and treatment of fibromyomatosis that "*There are many pharmacological strategies that can be used in the treatment of symptomatic uterine fibroids…In case of failure of medical therapies, the use of surgical techniques and alternative techniques may be indicated*" [19]. Therefore, in the third millennium healthcare providers must consider the global impact of UF and different treatments on individual women's lives. For example career women, women with family commitments aiming for better sexual health and even looking for pregnancy. The current

approach must take into account all women's needs, their daily problems, their fears and expectations, shifting from a lesion-oriented vision to a patient-oriented one [3].

New pharmacological approaches

The new tools for the medical management of UF currently at our disposal, the oral GnRH antagonists with add-back therapy (ABT), allow greater flexibility with safe options. The efficacy is based on the fast binding to the GnRH receptor, blocking endogenous GnRH activity with suppression of LH and FSH production, avoiding the initial increase observed with GnRH agonists and unwanted flare-up effects [3, 20]. Moreover, the ABT with oestrogen/progestin acts as prevention of the side effects of hypoestrogenism (mainly bone loss, hot flushes), and allow long-term use.

Relugolix Combination Therapy (40mg Relugolix + 1mg oestradiol as hemihydrate + 0.5mg norethisterone acetate), one tablet daily, is licensed for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age [21]. The triple combination has the aim of combining preventive activity on the growth of UF with the maintenance of oestradiol and progesterone levels in an optimal therapeutic range, in order to minimize the adverse effects [21–23]. In particular Relugolix, a phenylurea derivative, has an affinity 52 times higher for GnRH receptor in the anterior pituitary than endogenous GnRH [21, 24, 25], the oestradiol concentrations are maintained comparable to those in the early follicular phase of the menstrual cycle, thus preserving bone mineral density and significantly improving the patient's quality of life [21, 22] and finally the synthetic progestin norethisterone acetate is added to reduce the risk of oestrogen-induced endometrial hyperplasia [21]. The oestrogen threshold notion is very important because the "therapeutic window" (20-50 pg/ml) of circulating oestradiol concentrations allows a decreased myometrial and fibroid volume, but at same time bone resorption is preserved [26, 27].

In the phase 3 double-blind trials (LIBERTY 1 & LIBERTY 2) a higher proportion of women with UF and HMB respond with <80mL menstrual blood loss/cycle and at least a 50% reduction in the Relugolix CT group compared to placebo group (Fig. 1) with a similar incidence of adverse events. Moreover, the differences between Relugolix CT and placebo in achieving amenorrhoea, in improving haemoglobin levels when presenting with anaemia at baseline and in reducing uterine volume were all statistically significant [22].

Patient-reported outcome results provide additional evidence of the benefit of Relugolix-CT on the UF-associated symptom burden, including UF-associated pain, distress from key symptoms of UF (HMB, passing blood clots, and pelvic tightness or pressure), and HRQoL. Notably, women treated with Relugolix-CT experienced significant improvements in UF-related activities (including physical and social activities), energy/mood control, self-consciousness and sexual function compared with women receiving the placebo (Fig. 2) [28].

In addition, Relugolix CT is able to provide inhibition of ovulation in women taking the recommended dose and provides adequate contraception after at least one month of use [21].

BMD was preserved in the lumbar spine of women treated with Relugolix CT up to 104 weeks of treatment [21]. Therefore, the combination therapy with Relugolix CT, producing oestradiol concentrations of 33 pg/ml, as in an early follicular phase [21], within the therapeutic window, represents a balanced long-term treatment for women with HMB associated with UF.

Conclusions

The management of patients with myomas has changed substantially during the last century and probably will continue to do so. We must now take a holistic approach based on a strong interaction between the doctor and the patient. The ability of Relugolix CT to fight the most common and most troublesome symptoms associated with UF and the related distress, has practical implications in considering treatment options. Moreover, the very promising results described for UF in this paper may be extended in the near future also to other hormone-sensitive pathologies, such as endometriosis.

Compliance with Ethical Standards

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Disclosure of Interest

None of the authors have any conflicts of interest for the present manuscript.

In the past 36 months:

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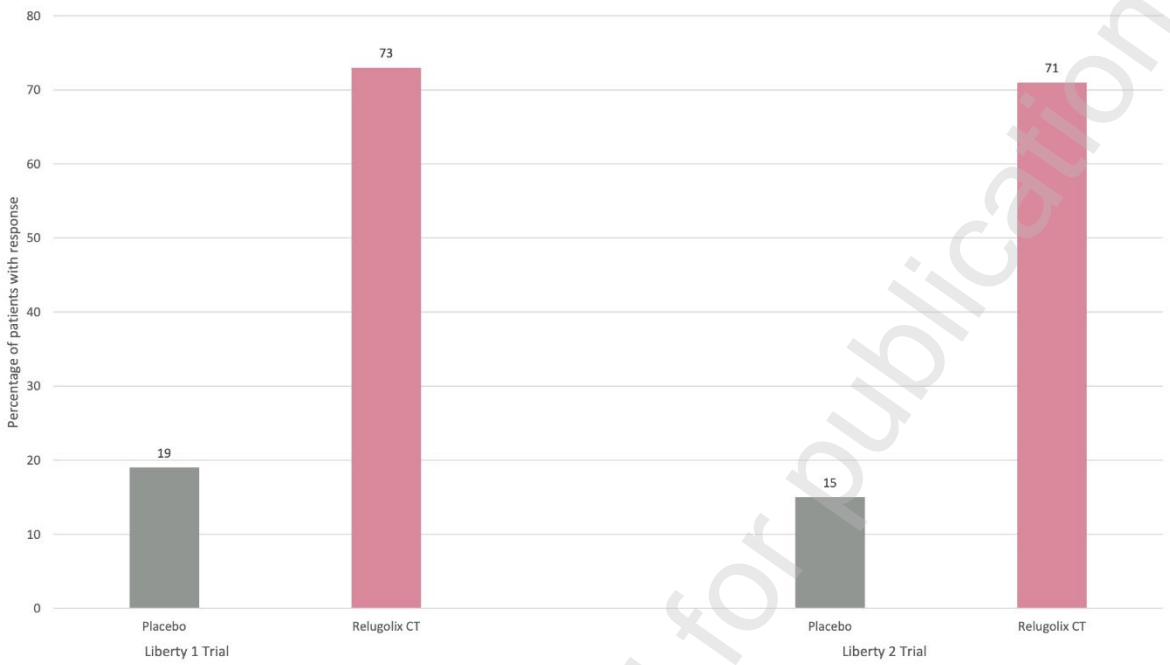
Table 1. Activities negatively affected by symptoms

ACTIVITIES AFFECTED	% OF WOMEN	95% CONFIDENCE INTERVAL
Sexual life	42.9%	(39.5-46.4%)
Performance at work	27.7%	(24.7-30.9%)
Relationship and family	27.2%	(24.2-30.4%)
Housekeeping	25.9%	(22.9-29%)
Attendance at work or university	24.4%	(21.5-27.5%)
Social activities	22.7%	(19.9-25.7%)
Sports	19.9%	(17.2-22.8%)
Type and colour of clothes to wear	16.0%	(13.6-18.7%)
None of the above	25.5%	(22.6-28.6%)

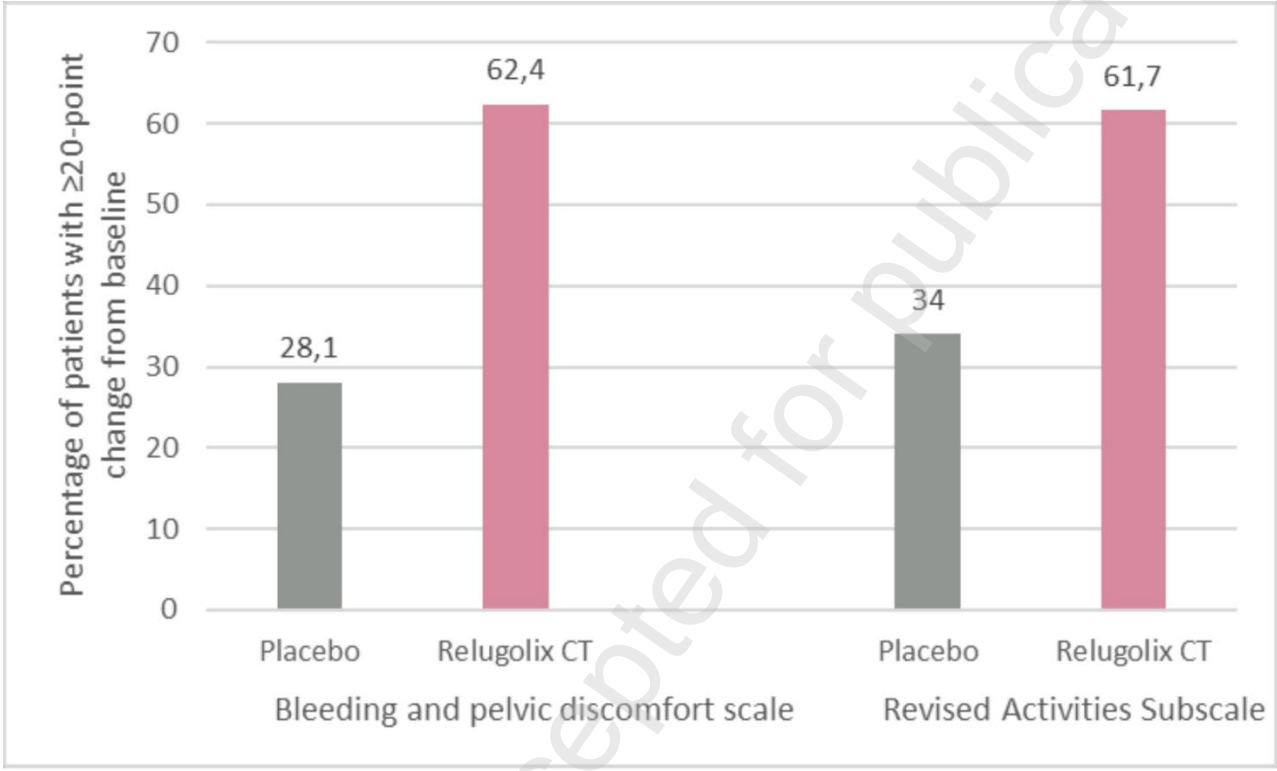
1.533 women with diagnosed uterine fibroids across 8 countries were asked about the impact of their symptoms on their daily life in the last 12 months. Those women who reported a mild to severe impact of symptoms were additionally asked which activities were negatively affected by their symptoms. (Zimmermann A. et al. 2012)[5]

Figure 1. Clinical trials: reduction in HMB



Results of the registrative trials of Relugolix-CT Liberty 1 and Liberty 2. The response was defined as a volume of menstrual blood loss < 80 ml and a reduction of at least 50% from the baseline, as measured by the alkaline hematin method, over the last 35 days of the treatment period. The primary end-point analysis in each trial was the comparison of Relugolix CT with placebo (p value < 0.001). (Modified from Al-Hendy A et al., 2021)[20]

Figure 2. Clinical trials: bleeding/pelvic discomfort scale and revised activities subscales



In the course of the registrative trials of Relugolix-CT Liberty 1 and Liberty 2, to assess the UF-specific patient experience, the UFS-QoL was administered in both studies and completed every 3 months. In addition to the original UFS-QoL scales and subscales, two additional endpoints were assessed: one of them focusing on distress from key UF symptoms and the other on impact on physical and social activities.

In a pooled analysis of the two trials the proportion of women showing a reduction of at least 20 points from baseline to week 24 on the BPD subscale was significantly higher with Relugolix-CT than with placebo (p value <.0001). Similarly, for the improvement of at least 20 points in the RA subscale (p<.0001). (Modified from Stewart EA et al., 2022)[26]