COMBINED RELUGOLIX TREATMENT FOR HIGHLY SYMPTOMATIC UTERINE LEIOMYOMA PATIENTS

B. I. Ștefănescu[1,3], T. I. Mihalache[1,3], Bianca Georgiana Constantin[2*], D. A. Chiran[4], C. I. Stan[4], A. A. Ionescu[1,3]
"Dunarea de Jos" University Galati, Faculty of Medicine and Pharmacy
1. Clinical Surgical Department
2. Department of Morphological Sciences
"Sf. Ap. Andrei" Clinical Emergency Hospital Galati, Romania
3. 2nd Clinic of Obstetrics and Gynecology
"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania
Faculty of Medicine
4. Department of Morpho-Functional Sciences (I)
*Corresponding author. E-mail: bianca.constantin@ugal.ro

COMBINED RELUGOLIX TREATMENT FOR HIGHLY SYMPTOMATIC UTERINE LEIOMYOMA PATIENTS (Abstract): Many conservative treatments for symptomatic uterine leiomyoma have been proposed but in the large majority of cases these are often limited by the associated side effects. A relative novel treatment with GnRH antagonists has been reported in the literature with good results. The primary goal was to assess the degree of reduction of uterine global volume and largest uterine fibroma volume at the end of 24 weeks of combined treatment with Relugolix 40 mg, 1 mg estradiol and 0.5 mg norethindrone acetate as well as at 12 weeks after. The secondary goal was to subjectively assess the reduction of vaginal bleeding during treatment and the evolution of hematologic parameters. **Materials and methods:** We analyzed 5 patients with uterine leiomyoma with heavy menometrorrhagia and severe anemia. 4 cases rejected the surgical treatment and 1 case was not suitable for surgery due to morbid obesity and associated pathology. All cases accepted the combined therapy with relugolix 40 mg, 1 mg estradiol and 0.5 mg norethindrone acetate for a period of 24 weeks. **Results:** In all cases, the reduction of uterine and largest leiomyoma volume was consistent after 24 weeks of treatment and maintained so even 12 weeks after. In addition, the severity of vaginal bleeding was also reduced, so that the hematologic parameters slowly improved. **Conclusions:** Combined therapy with relugolix 40 mg, 1 mg estradiol and 0.5 mg norethindrone acetate is a very good alternative especially in cases where surgery is not accepted or is not suitable due to associated morbidity. **Keywords:** LEIOMYOMA, MENOMETRORRAHAGIA, SEVERE ANEMIA, RELUGOLIX.

INTRODUCTION

Uterine leiomyoma, known in medical practice as uterine fibroid, is the most common form of benign tumor of the uterus. It is also known that the prevalence of this tumor reaches its maximum rates among women in the reproductive period (15-50 years old women) (1, 2) and its development and growth is highly dependent of hormonal factors; throughout

life, approximately two out of three women, especially between 30 and 50 years of age, will develop this type of pathology (3).

Cases of uterine fibroids in the prepubertal period have not been described in literature, and cases found among teenage girls have rarely been found. The maximum incidence is found among Afro-American women in their fifties. In Caucasian population, the incidence is reached by women the ages of 30 and 40. Currently, there is not enough information to clarify the rate of occurrence of uterine fibroids among Hispanic and Asian women (4).

The incidence of these tumors is firstly connected to the hormonal activity (5) and this is sustained by the association of this pathology with nulliparity/infertility, early menarche and late menopause. Heredity, race and age are also important risk factors (5). Other risk factors such as heart disease, especially hypertension, smoking, alcohol consumption, oxidative stress, have not been sufficiently documented.

This pathology is often neglected by patients, many of them are presenting with large pelviabdominal tumors, heavy vaginal bleeding and severe anemia.

Although the definitive treatment remains hysterectomy, conservative treatments are recently widely accepted, and these are mostly sustained by the desire of the patients to preserve the uterus and thereby fertility. The main goals of the conservative treatment are to reduce the symptoms and to diminish the size of the leiomyomas (6).

Despite being the first-line medical treatment for uterine fibroids, there is little evidence to support the use of contraceptives (7).

Although leuprolide acetate and other injectable long-acting gonadotropin-releasing hormone (GnRH) agonists (8) are effective, their duration of use is limited by hypoestrogenic sequelae, which may need the use of supplementary hormonal therapy to offset adverse effects.

The selective progesterone-receptor modulator - ulipristal acetate - is recommended by the European Medicines Agency to be used for the treatment of uterine fibroids only in premenopausal women in whom surgical procedures (including uterine fibroid embolization) are not appropriate or have not worked. However, its use must be very cautious since there are reported rare cases of serious liver injury (9).

The GnRH antagonist elagolix is licensed for the treatment of uterine fibroids for a period of 24 months and lowers excessive menstrual flow in women with uterine fibroids when taken with estradiol and norethindrone acetate (10). However, due to its short half-life, elagolix must be taken twice daily. Its use has been linked to negative effects on blood pressure, cholesterol and liver enzyme levels, and bone mineral density at one year (10, 11).

Relugolix and linzagolix are new GnRH antagonists which have been demonstrated high efficiency in the treatment of symptomatic leiomyoma patients (12, 13).

MATERIALS AND METHODS

This study reflects our experience with combined relugolix therapy for highly symptomatic uterine leiomyoma patients.

Our case series included five patients that addressed to Obstetrics and Gynecology 2nd Clinic, “Sf. Ap. Andrei” Clinical Emergency County Hospital Galati, between the 1st of November 2023 and 31st of March 2024 for heavy vaginal bleeding and

severe anemia due to large uterine leiomyomas. After initial assessment, in all cases dilatation and curettage (D&C) with hemostatic and bioptic indication was performed along with hematologic reanimation (in three cases blood transfusions were indicated).

Ultrasound endovaginally scan was performed in all cases using a *General Electric Voluson* S8 equipment. Uterine volume as well as the volume of the largest leiomyoma were noted in all cases.

Surgical treatment - total hysterectomy - was proposed and categorically refused by 3 patients. In the remaining two cases, due to morbid obesity sustained by BMI above 40, conservative treatment was our first choice.

All five cases in our study were treated with a combination of relugolix 40 mg, 1 mg estradiol and 0.5 mg norethindrone acetate for 24 weeks. The patients were clinically and ultrasonographical assessed at the beginning of the trial, at the end of the pharmacological treatment in week 24, and again 12 weeks from stopping the treatment.

RESULTS

The cases under investigation were white female, 42 to 50 years of age. Body mass index (BMI) was above 30 in all cases (mean 39.74 ± 5.03). In 2 patients, in which associated morbidity such as diabetes or cardiac disease were also noticed, the BMI was even above 40 (tab. I).

TABLE I.

Clinical and paraclinical features of the cases.

BASELINE CHARACTERISTICS	Case 1	Case 2	Case 3	Case 4	Case 5
Age(years)	42	48	50	46	49
Race	White	White	White	White	White
Region	Europe	Europe	Europe	Europe	Europe
BMI (kg/m^2)	33.4	36.7	45.8	39.2	43.6
MBL - (No. of pads/tampons)					
0 w	10	9	12	11	12
24 w	5	7	7	8	7
36 w	4	7	6	7	6
Uterine volume (cm^3)					
0 w	210.23	390.73	449.89	381.47	472.9
24 w	186.8	320.7	387.8	317.6	394.1
36 w	172.5	304.9	367.2	308.5	379.4
Volume of largest leiomyoma (cm^3)					
0 w	53.52	85.76	112.69	66.1	113.92
24 w	41.6	63.8	79.2	49.6	75.6
36 w	39.7	58.5	71.4	43.8	67.8
Hemoglobin concentration (g/dL)					
0 w	7.8	8.5	5.7	8.2	6.8
24 w	9.6	9.8	9.2	9.7	9.4
36 w	9.8	10.1	9.6	10.0	9.8

BMI - body mass index; MBL - menstrual blood loss.

All cases presented with a history of severe menstrual and/or intermenstrual bleeding, which was subjectively assessed by the number of absorbent pads used daily. In our group, the number of pads used in the heaviest day of vaginal bleeding was between 9 to 12 per day. During the combined treatment with relugolix, the number of pads used was progressively lower so that, at the end of 24 weeks of treatment this number ranged between 5 to 8. Moreover, 12 weeks after the initial treatment, vaginal bleeding was reasonable, with a number of absorbent pads between 4 to 7 daily (tab. I).

The reduction of vaginal bleeding along with the hematological treatment were the key factors for correction of severe anemia. At the start of the trial, the patient's hemoglobin levels ranged between 5.7-8.5 g/dL (mean 7.4 ± 1.14). After 24 weeks of combined treatment the hemoglobin values improved, ranged between 9.2-9.8 g/dL (mean 9.54 ± 0.24), and maintained above 9.6 g/dL (ranged between 9.6-10.1 g/dL, mean 9.86 ± 0.19) at 12 weeks after stopping the treatment (tab. I).

Positive outcomes were additionally noticed in terms of uterine global volume and the volume of the largest uterine leiomyoma (figs. 1, 2).

When combined therapy with relugolix was initiated, the global uterine volume of the cases ranged between 210.23 and 472.9 cm^3 (mean 381.04 ± 103.01) and the greatest leiomyoma's volume between 53.52 and 113.92 cm^3 (mean 86.39 ± 27.12). A decrease of the global uterus volume was recorded in all cases with limits between 37.73 and 93.5 cm^3. Additionally, compared to day 0, the greatest leiomyoma's volume was much smaller at week 36, with values between 39.7 and 71.4 cm^3, the range of recorded reduction being between 13.82 to 46.12 cm^3 (tabs. I, II, figs. 1, 2).

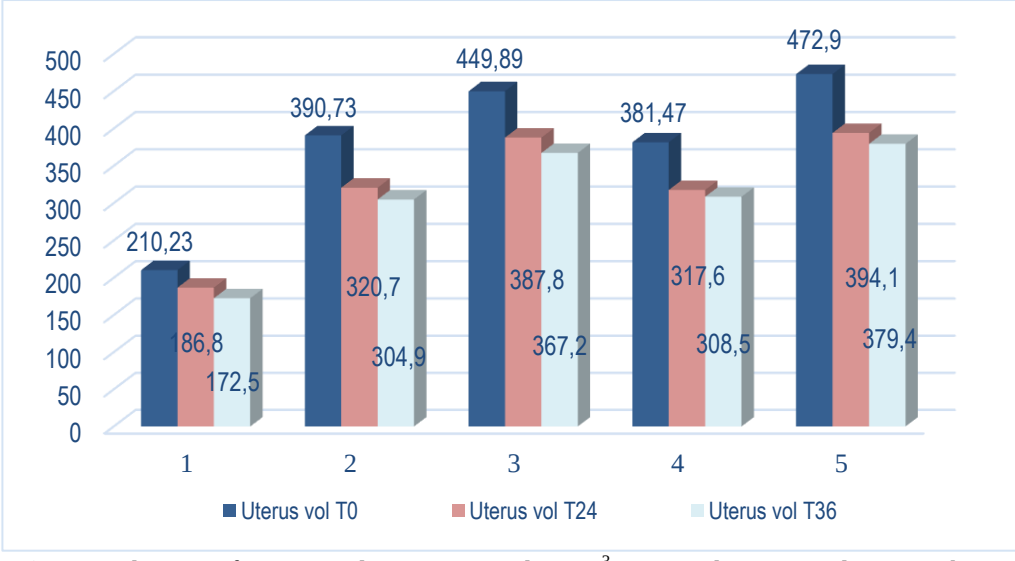

Fig. 1. Reduction of uterine volume expressed in cm^3 at 24 and respectively 36 weeks from the beginning (T0) of combined therapy with relugolix.

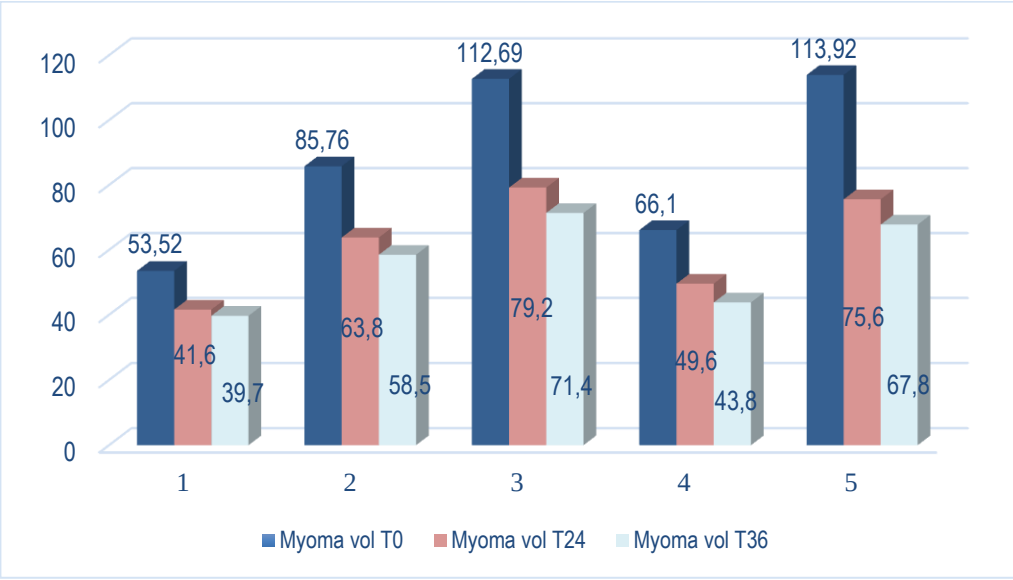

Fig. 2. Volume reduction of the largest uterine leiomyoma expressed in cm^3 at 24 and respectively 36 weeks from the beginning (T0) of combined therapy with relugolix.

TABLE II.

Study results evaluated at the beginning of treatment (T0), after 24 weeks (T24) of combined therapy, and after 36 weeks (T36) from the enrolment.

	TIME OF EVALUATION		
CHARACTERISTICS	**T0**	**T24**	**T36**
Uterine volume (cm^3)	381.04 ± 103.01	321.4 ± 83.4	306.5 ± 82.09
Volume of the largest uterine myoma (cm^3)	86.39 ± 27.12	61.96 ± 16.23	56.24 ± 14.11
Hemoglobin concentration (g/dL)	7.4 ± 1.14	9.54 ± 0.24	9.86 ± 0.19
Values are expressed as mean ± SD			

The treatment was well tolerated by the patients, none of them reported significant side effects.

DISCUSSION

Current studies regarding the conservative treatment of highly symptomatic uterine leiomyoma focus on the use of relugolix. This is a GnRH receptor antagonist that can be administered in daily doses and has the effect of blocking the binding and signaling of endogenous GnRH and thus leading to reversible, dose-dependent decreases in gonadotropin concentrations and subsequent suppression of the ovarian production of estradiol and progesterone.

Following two international studies, LIBERTY 1 and LIBERTY 2, that used combined therapy (relugolix, estradiol and norethindrone acetate) with daily administration, a significant decrease in menstrual bleeding was observed compared to the placebo group (12). Specifically, according to Al-Hendy *et al*, more than 70% of wom-

en with heavy uterine bleeding enrolled have reported a significant reduction of menstrual bleeding. Compared with placebo group, the mean reduction of menstrual blood loss was as much as 84.3% (12). Despite the fact that we did not used an objective method to quantify the amount of menstrual blood lost, the subjective assessment based on number of pads or tampons used in the heaviest day of menstrual bleeding suggests the same positive effect of the therapy.

The reduction of significant vaginal bleeding along with specific hematological treatment should eventually correct the anemic syndrome and thus, assuring a better physical condition for the patients. As we found in our study, other reports from the literature emphasize the significant increase in hemoglobin levels after relugolix combined therapy. In a recent observational study, Muzii *et al.* reported an increase in hemoglobin levels by 25% after 3 months of combined therapy, from 9.3 ± 1.1 to 11.6 ± 1.7 g/dL (14).

Moreover, after 24 weeks of relugolix combined therapy, patients should experience not only an improvement in the quality of life by reducing symptoms related to pelvic pain, heavy menstrual bleeding, oxidative stress but also an improvement in sexual life (12).

As in case of GnRH agonists (15, 16, 17), the use of GnRH antagonists with a concomitant hormonal add-back therapy has the same effect in reduction of uterine as well as myoma volumes but with less secondary effects associated with hypoestrogenism (14).

In a recent multicentric observational study published by Muzii *et al.*, the reduction of mean uterine volume after 3 months of combined relugolix therapy was as much as 26%. In addition, the reduction in diameter of the largest myoma was noted as much as 14% (14).

Although limited by the number of cases, our study reports near similar results. The mean uterine volume decreased from 381.04 ± 103.01 cm^3 at the enrolment to 321.4 ± 83.4 cm^3 after 24 weeks of combined treatment, corresponding to a 15.6% decrease, and again to 306.5 ± 82.09 after another 12 weeks of surveillance, corresponding to a 19.56% decrease. Moreover, the mean largest myoma volume decreased from 86.39 ± 27.12 cm^3 at the enrolment to 61.96 ± 16.23 cm^3 after 24 weeks of treatment, corresponding to a 28.27% decrease, and again to 56.24 ± 14.11 cm^3 after another 12 weeks of surveillance, corresponding to a 34.89% decrease. Despite the fact that reductions in uterine as well as in myoma`s volume were recorded in all patients, the most important degree of reduction noticed in our group was in patients with the largest uterus and largest myomas.

Moreover, the more significant degree of reduction of the uterine myomas when compared to the degree of reduction of global uterine volume could be explained by the very well-known facts that both estradiol and progesterone are essential for myoma development and these tumors are more responsive to sex steroids than normal myometrium (18).

We are in consensus with other recent reports from the literature on the fact that relugolix combined therapy could be used as a presurgical treatment as well, in order to reduce the volume of the uterus and myomas and thus to enable an improved surgical field, a less invasive surgical procedure or even postpone or amend the surgical treatment at all. In a recent study

from the literature, from the total number of 31 patients scheduled for surgery because of abnormal uterine bleeding associated with uterine myomas enrolled, in 4 patients (13%) the surgical procedure was shifted after 3 months of relugolix combined therapy to a less invasive approach (hysteroscopic myomectomy and laparoscopic hysterectomy) whereas in 8 patients (26%) the surgical treatment was temporarily avoided in favor of medical therapy for another 3 additional months (14).

Recent trials focus on efficacy and safety of long-term relugolix combined therapy. In a recent report published by Al-Hendy *et al*, from a total of 610 patients who were enrolled and completed LIBERTY trials, a number of 363 patients completed an additional 28 weeks of relugolix combined therapy (19). The reported results were very good and encouraging. 87.7% of patients with continuous 52 weeks of combined therapy had a sustained improvement in menstrual bleeding. Additionally, long-term combined therapy was also associated with a sustained reduction of other uterine leiomyoma symptoms and with a modest but continued reduction of uterine and leiomyoma volumes at week 52 when compared with week 24 of treatment (19). According to the same study, long-term relugolix combined therapy was generally well tolerated, headaches and hot flushes being the most frequent reported side effects (19).

CONCLUSIONS

Relugolix combined therapy proved to be very effective in patients with heavy vaginal bleeding associated with uterine leiomyomas. Clinical symptoms and anemic syndrome are significantly reduced after 24 weeks of treatment and maintained so even 12 weeks after. This therapy should always be taken into consideration in highly symptomatic leiomyoma patients who do not agree or are not suitable with surgical management or as preoperative medical treatment in order to reduce the uterine and myomas volumes and thus assuring a safer and perhaps more conservative approach. Despite our little number of cases, the results are similar to other reports from the literature. More studies have to be done in order to establish the efficacy and safety of long-term treatment.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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