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Review Article

Effect of Ulipristal Acetate on Uterine Fibroid Angiogenesis, Measured by 2D Power Doppler Ultrasound and Serum VEGF Levels

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Abstract

Introduction: Uterine fibroids are a frequent pathology in women of reproductive age responsible for a variety of symptoms that can become disabling. Ulipristal Acetate is a medical treatment that causes a decrease in the size of the fibroid, improving symptoms. In this study we evaluated the correlation between the vascularization of the fibroid measured by ultrasound (Power Doppler 2D) and the levels of VEGF in serum, before and after treatment with ulipristal acetate in patients diagnosed with symptomatic uterine fibroids.

Material and Method: A prospective observational study was designed. Twenty-four premenopausal women, previously diagnosed with symptomatic uterine fibroids, were included and all completed the study. Four cycles of Ulipristal Acetate were administered according to the dose and indications specified in the data sheet. To assess the influence of this treatment on the fibroid angiogenesis process, serum VEGF levels were measured and its vascularization was assessed by 2d Power Doppler ultrasound; at the beginning and at the end of treatment. In addition, in successive visits several determinations of the same parameters were made. Parameters were defined as the decrease in VEGF levels from previous levels,

Results: 24 patients who met the inclusion criteria (n = 24) were recruited. The average size of the fibroids was reduced from 45.08 ± 24.02 mm to 29.00 mm-+-16.96 mm after treatment. The mean serum level of VEGF decreased significantly after the first cycle of treatment (from 147.17 ± 153.51 pg/mL to 102.04 ± 186.08 pg/ml). The vascularization of the fibroids was analyzed after treatment with Ulipristal Acetate, and a significant decrease was achieved in 83.3% of the cases.

Conclusions: There is a correlation between decreased vascularization of fibroids and treatment with Ulipristal Acetate. Selective Progesterone Receptor Modulators can provide effective treatment for women with symptomatic fibroids in two ways: by blocking selective progesterone receptor modulators and by reducing angiogenesis.

Keywords: Angiogenesis; Ulipristal Acetate; Uterine Fibroids; VEGF Doppler Ultrasound

Abbreviation

VEGF: Vascular Endothelial Growth Factor; 2D: Two Dimensions; MSRP: Selective Progesterone Receptor Modulator

Key Message

We demonstrate the action of Ulipristal Acetate on fibroid angiogenesis, through the reduction of serum VEGF levels and vascularization changes observed with 2D Power Doppler ultrasound. These changes are significant, and are maintained over time.

Introduction

Uterine fibroids are the most common benign tumor in women of reproductive age, with a clinically significant prevalence of 20% with peaks of 40% in women between 35 and 55 years of age. They originate in the muscle cells of the uterine wall, they are often multiple and their size varies from millimeters to several centimeters, being able to cover the entire uterine volume and reaching a significant weight [1]. Although the ultimate etiology of their development is unknown, the growth of fibroids is influenced by female sex hormones (estrogens and gestagens) since their size normally increases during pregnancy and the reproductive stage and decreases during menopause [2].

Most uterine fibroids are asymptomatic and do not require any type of treatment, but they have a great negative impact on the physical and emotional well-being of those women who develop symptoms. These may be related to changes in bleeding pattern (irregular or prolonged bleeding, between periods, or excessive bleeding with secondary anaemia), pelvic discomfort (due to compression of adjacent organs such as the bladder, bowel, or ureters), pelvic pain caused by anatomical distortions of the uterus, infertility or difficulties in conception, implantation of the embryo, development of pregnancy (the presence of fibroids can increase the risk of miscarriage and premature birth) and childbirth. 62% of women who have symptoms have more than one [2,3].

Classically, the treatment of fibroids has been the surgical removal of the fibroid (myomectomy) or the uterus (hysterectomy), but many women do not want to lose the uterus, regardless of whether or not their reproductive life has ended. Several studies have confirmed the efficacy and safety [4] of intermittent and repeated long-term treatment with ulipristal acetate (5 milligrams) in patients with symptomatic uterine fibroids. This drug has shown good tolerability and the ability to rapidly reduce bleeding, reduce the volume of fibroids, and improve the level of pain and quality of life of the patient.

The mechanism of action of this drug is based on the selective blockade of progesterone receptors, a hormone involved in the pathogenesis of fibroids [6,7].

Although uterine fibroids are benign tumors, angiogenesis is critical for their growth and development. Vascular endothelial growth factor (VEGF) plays a very important role in its growth and could be used as a marker of disease activity and possible prognostic factor [8-10].

VEGF-A is significantly prevalent in uterine fibroid tissue, compared to the adjacent myometrium [8].

The objective of this study is to evaluate the effect of treatment with ulipristal acetate on its vascularization, measured by ultrasound (Power Doppler 2D), and angiogenesis, determined by blood VEGF levels.

As a secondary objective, it will be checked if there is a decrease in uterine fibroids.

Material and Methods

Prospective, observational study, carried out between October 2017 and February 2020 in the Gynecology Unit of the García Orcoyen Hospital in Estella (Navarra). Patients with symptomatic uterine fibroids (hypermenorrhea, pain and pressure), candidates for treatment with ulipristal acetate, were included in the study. Patients with an indication for surgical treatment or with a contraindication for treatment with ulipristal acetate, and those who could not attend the follow-up visits were excluded. All the patients finally included in the study agreed to participate in it and signed the informed consent. The study was approved by the Navarre Drug Research Ethics Committee.

Ulipristal acetate was used under normal clinical practice conditions, in accordance with the indication established in its approved data sheet (dose of 5 mg per day for three months, repeated for four cycles with a rest period of 2-3 months between each cycle. The recommendations given by the Spanish Medicines Association in February 2018 on the suspension of treatments with ulipristal acetate were followed, with the repercussion in the study of the increase in waiting time between cycles (1 month), until the prescription was restarted in August 2018. All patients included in the study underwent a thorough history and liver profile was analyzed before starting treatment, and were monitored at the start of each of the four treatment cycles, in accordance with the recommendations of the European Pharmacovigilance Risk Assessment Committee (PRAC).

Each patient attended a first visit in which her demographic data (age, weight, height) and all the information related to the patient's gynecological history were recorded, including confirmation of the ultrasound diagnosis of one or more symptomatic uterine fibroids, classification (FIGO criteria), size and symptoms, as well as the existence of concomitant treatments and the result of the pregnancy test. The study methodology was explained and informed consent was obtained.

Four more visits were made, one at the beginning of each treatment cycle with ulipristal acetate. A blood test was performed in which serum VEGF levels (pg/mL) were determined by sandwich ELISA method with monoclonal antibody (Human VEGF Immunoassay, Quantikine, R&D Systems, Minneapolis, USA).

The ultrasound examination, which allows the size of the fibroid to be measured with great precision, to recognize the number of fibroids and to assess the degree of vascularization, was performed transvaginally with the patient in the lithotomy position, with a 15º head elevation. on the horizontal and with an empty bladder at the beginning and end of the treatments. All examinations were performed by a single investigator (MGM) with more than fifteen years of experience, with the Voluson 730-PRO ultrasound system equipped with a vaginal probe enabled to obtain information in B-mode, color map and pulsed Doppler.

2D power Doppler ultrasound allowed the size of the fibroid to be measured(maximum diameter) at the beginning and at the end of treatment, and the percentage of fibroids that decreased in size was calculated.

Ultrasound also made it possible to observe the vascularization of the fibroids and classify it as low if it affects less than 25% of the circumference of the fibroid, moderate if it is between 25-50%, and high if it affects more than 50%. The degree of vascularization was analyzed at the beginning and at the end of treatment.

The quantitative variables of the study were described with the mean and standard deviation (SD) or with the median and interquartile range (IQR), maximum and minimum, and the categorical variables as frequencies and percentages. The correlation between the degree of vascularization and VEGF levels before and after treatment with ulipristal acetate was studied. The size of the fibroid and serum levels of VEGF before and after treatment with ulipristal acetate were compared using Student's t test. and the decrease in size and vascularization by Pearson's Chi-square, considering a $p < 0.05$ as significant. The calculations were made with SPSSv.25.

Results

In this study, 43 women diagnosed with symptomatic uterine fibroids who underwent medical treatment with ulipristal acetate were included. 3of them left the study after the first cycle, four after the second and two after the third, voluntarily without producing any adverse effect.

The mean age of the patients was 45.4 years (SD = 5.37), with a range of 18 to 52 years. The BMI was 23.25 kg/m^2 (SD = 4.71), the mean weight was 61.34 kg (SD 10.37) and the height was 162.43 cm (SD = 4.83). None of the participants used concomitant medication and no other gynecological disease was observed. All patients had a negative pregnancy test result.

The most frequent symptom was hypermenorrhea (90%), followed by pelvic pain (7%) and asthenia secondary to chronic anemia (3%).

From the ultrasound point of view, the fibroids presented a rounded structure, well limited with respect to the adjacent myometrium, with different characteristics of echogenicity. In general, they were homogeneous, although on occasions calcifications (%), hemorrhages (%) or cystic areas (%) could be seen. Single fibroids (%) were easily located, but in x (%) cases of fibroids, the uterus was so deformed that it was difficult to delineate its contour and cavity.

Myomas are benign tumors, with very little vascularization, which in their development, displace normal vessels towards the periphery.

The vast majority (DAR %) of the fibroids had a vascularization located in the tumor periphery and the flows were of high resistance (Figure).

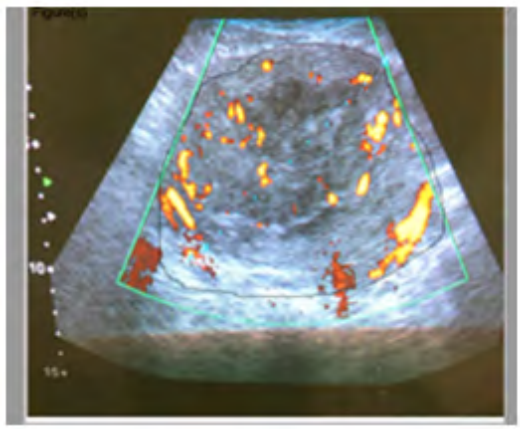

Figure 1: Exploration ultrasound. Different types of vascularization.

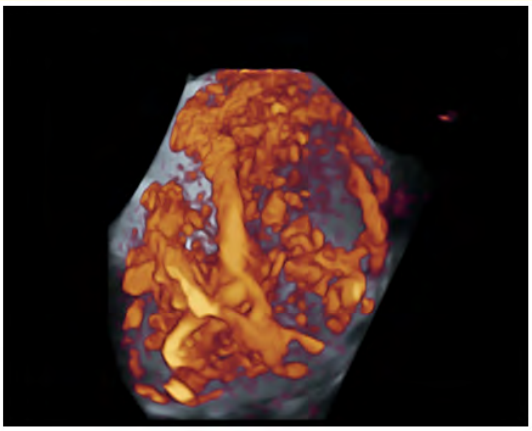

Figure 2: Abundant vascularization.

Mean fibroid size at the start of ulipristal acetate treatment was 44.87 mm +_SD 23 mm (range 10 to 100 mm); After 20 months, at the end of treatment, the mean size was reduced to 29 mm (SD: 16.9).

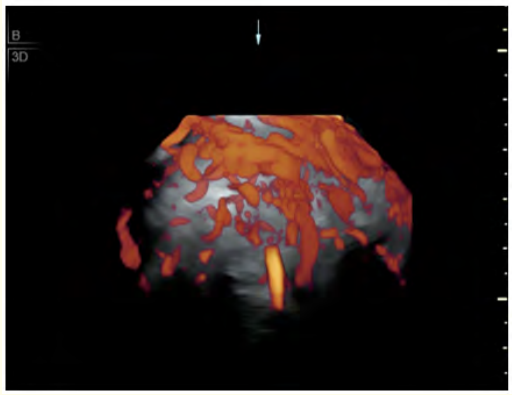

Figure 3: Moderate vascularization.

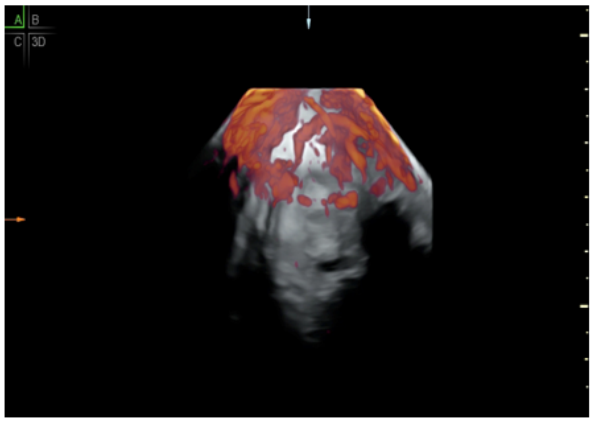

Figure 4: Vascularization escasa.

The mean serum level of VEGF decreased by 30% after treatment (from 147.17 pg/ml, SD: 153.51 to 102.04 pg/ml SD: 183.08, p = 0.0001.

Vascularization was analyzed of fibroids after treatment with ulipristal acetate, and a significant decrease was achieved in 83.3% of cases. Only in 16.7% there was no decrease in vascularization (Table 1).

		Frequency (n)	Percentage %	Valid Percentage %	Accumulated percentage %
Valid	Decrease	4	16.7	16.7	16.7
	No decline	20	83.3	83.3	100.0
	Total	24	100.0	100.0	

Table 1

Table 2 Effect of treatment with AdeU on the different variables under study. Variables under study before and after treatment with AdeU.

	N	Lower limit	Upper limit	Half	Typical deviation
Age (years)	24	33.00	52.00	45,4583	4.22188
Size before treatment (mm)	24	10.00	100.00	44.8750	23.52300
Valid N	24				

Table 2: Mean age of the patients. Mean size of the fibroids at the beginning of the study. Descriptive statistical data.

		Half	N	Typical deviation	Typical error
Pair1	Size 1 (mm)	45.0870	24	24.02823	5.01023
	Size 2 (mm)	29,0000	24	16.96788	3.53805
Pair2	VEGF1 p/mL	147,1739	24	153.51004	32.00906
	VEGF2 pg/mL	102.0435	24	183.08629	38.17613

Table 3: Paired sample statistics. Size 1: Size of the fibroids at baseline. Size 2: Size of fibroids after treatment with ulipristal acetate. VEGF1: Serum level of VEGF at baseline. VEGF2: Serum level of VEGF after treatment. The data reflect the average of the difference between the two measures calculated for each patient.

		N	Correlation	p
Pair1	Size1 and Size2	24	.865	,000
Pair2	VEGF1 and VEGF2	24	,694	,000

Table 4: Matched sample correlation. The suffix "1" refers to the measurement at the beginning of the study. Suffix "2" refers to measurement after 4 treatment cycles. There is a statistically significant correlation between the decrease in the size of the fibroid and the decrease in vascularization.

Half		Paired samples					YOU	GL	Next (2-sided)
		Typical deviation	Typical error	Confidence Interval of 95%					
				lower	Higher				
Pair1	Size1 – Size2	16.08696	12.63082	2.63371	10.62498	21.54893	6,108	22	,000
Pair2	VEGF1 – VEGF2	45.13043	134.47247	28.03945	-13.01982	103.28069	1,610	22	.122

Table 5: Paired sample test. The suffix "1" refers to the measurement at the beginning of the study. Suffix "2" refers to measurement after 4 treatment cycles.

		Frequency (n)	Percentage %	Valid Percentage %	Accumulated percentage %
Valid	Decrease	4	16.7	16.7	16.7
	No decline	20	83.3	83.3	100.0
	Total	24	100.0	100.0	

Table 6: Decreased vascularization.

Discussion and Conclusion

This work demonstrates, *in vivo*, the efficacy of treatment with ulipristal acetate on the VASCULARIZATION levels of fibroids measured by 2D Doppler ultrasound and the determination of serum VEGF levels before and after treatment with ulipristal acetate.

The results obtained in this study show that ulipristal acetate produces a decrease in the size of fibroids 3 in addition to a decrease in angiogenesis measured by 2D Doppler ultrasound and serum levels of VEGF [8].

In recent years, angiogenesis and vascularization have become a fundamental part of the study of tumor growth. In the case of uterine fibroids, it has been found that there are differences in vascularization when compared to the adjacent uterine tissue. This dysregulation of angiogenesis could clarify the pathophysiology of this very common entity and, at the same time, help in the development of new treatments [7,8].

One of the basic building blocks of angiogenesis and the angiogenic process is vascular endothelial growth factor, or VEGF. Several recent studies have shown higher levels of VEGF in fibroid tissue compared to the adjacent myometrium, suggesting that angiogenesis plays a key role in fibroid development and growth [9].

Until a few years ago, the treatment of fibroids was fundamentally surgical, with the complications that it entailed, and medical treatment was fundamentally aimed at correcting anemia prior to surgery.

Currently, the paradigm of treatment of fibroids has changed, indicating individually what type of treatment is optimal depending on the symptoms and personal circumstances of each patient. One of the protagonists of this change has been ulipristal acetate, which has shown high efficacy in reducing uterine fibroids by blocking progesterone receptors. This type of drug has demonstrated its ability to reduce the levels of VEGF receptors in cultured uterine cells, which presupposes an antiangiogenic effect [10].

We can conclude that ulipristal acetate has a double effect on fibroids, through blockade of progesterone receptors and through the decrease in vascular endothelial growth factor, directly responsible for the angiogenic phenomenon.

However, more long-term studies are needed to measure the effect of ulipristal acetate on ultrasound-measured vascularization levels and VEGF levels.

The work published by Reshef Talen., *et al*. [8], refers to the role of angiogenic factors in the pathogenesis of fibroids. Angiogenesis has been extensively studied in numerous neoplastic processes, contributing to the research and development of new antiangiogenic therapeutic pathways [10,11].

Regarding benign entities, there are no *in vivo* investigations to determine the effect of these antiangiogenic drugs, mainly due to the high cost and the possibility of side effects. This cannot lead to a false interpretation that the angiogenic phenomenon is not involved in the pathogenesis of these entities.

In previous studies, we showed that ovarian endometriosis and its symptomatology were directly related to angiogenesis [12-14].

The relationship of fibroids with angiogenesis is well defined mediated by the action of VEGF [14-16].

In the reviewed literature, ulipristal acetate is directly involved in the angiogenesis of myoma cells in *in vitro* studies. However, to date, no one has analyzed in daily clinical practice whether treatment with ulipristal acetate causes not only progesterone receptor blockade, but also a decrease in fibroid angiogenesis as measured by Doppler ultrasound analysis of the heart. VEGF serum. Our study demonstrates for the first time how ulipristal acetate significantly decreases angiogenesis in uterine fibroids.

Bibliography

1. Gupta S., *et al*. "Clinical Presentation of fibroids". *Best Practice and Research Clinical Obstetrics and Gynaecology* 22.4 (2008): 615-626.

2. Olufowobi O., *et al*. "Are the anticipated benefits of myomectomy achieved in women of reproductive age? A five-year review of the results at a tertiary hospital". *Journal of Obstetrics and Gynecology* 24 (2004): 434-440.

3. Donnez J and Dolmans MM. "Uterine fibroid management: from the present to the future". *Human Reproduction Update* 22.6 (2016): 665-686.

4. Stovall DW., *et al*. "Clinical symptomatology of uterine leiomyomas". *Clinical Obstetrics and Gynecology* 44 (2001): 364-371.

5. Esmya® 5 mg data sheet. Date of first authorization: February 23 (2012).

6. Donnez J., *et al*. "The place of selective progesterone receptor modulators in myoma therapy". *Minerva Ginecologica* 68.3 (2016): 313-320.

7. Rabe T., *et al*. "Selective Progesterone Receptor Modulators for the Medical Treatment of Uterine Fibroids with a Focus on Ulipristal Acetate". *Biomed Research International* 2018 (2018): 1374821.

8. Mostafa A Borahay., *et al*. "Signaling Pathways in Leiomyoma: Understanding Pathobiology and Implications for therapy". *Molecular Medicine* 21 (2015): 242-256.

9. Minah Kim., *et al*. "VEGF-A regulated by progesterone governs uterine angiogenesis and vascular remodeling during pregnancy". *EMBO Molecular Medicine* 5 (2013): 1415-1430.

10. Juan Luis Alcázar and Manuel García Manero. "Ovarian endometrioma vascularization in women with pelvic pain". *Fertility and Sterility* 87.6 (2007).

11. Reshef Tal and James H Segars. "The role of angiogenic factors in fibroid pathogenesis: potential implications for future therapy". *Human Reproduction Update* 20.2 (2014): 194-216.

12. Juan Luis Alcázar., *et al*. "Vascular endothelial growth factor (VEGF) and ovarian endometriosis: correlation between VEGF serum levels, VEGF cellular expression, and pelvic pain". *Fertility and Sterility* 88.2 (2007).

13. Czuczwar P., *et al*. "Influence of ulipristal acetate therapy compared with uterine artery embolization on fibroid volume and vascularity indices assessed by three-dimensional ultrasound: prospective observational study". 45.6 (2015): 744-750.

14. Nieuwenhuis LL., *et al*. "Fibroid vascularization assessed with three-dimensional Power Doppler ultrasound is a predictor for uterine fibroid growth: a prospective study". *BJOG* (2017).

15. Peng Yu., *et al*. "Progesterone-mediated angiogenic activity of endothelial progenitor cell and angiogenesis in traumatic brain injury rats were antagonized by progesterone receptor antagonist". *Cell Proliferation* 50.5 (2017): e12362.

16. Anita Olejek., *et al*. "Long-term intermittent pharmacological therapy of uterine fibroids – a possibility to avoid hysterectomy and its negative consequences". *Prz Menopauzalny* 15.1 (2016): 48-51.