MANAGEMENT OF THE MEDICAL THERAPY OF UTERINE FIBROSIS

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Abstract: *Starting with the observation that fibroid growth is hormone dependent, current medical treatments mainly involve hormonal manipulation. Gonadotrophin-releasing hormone analogues (Gn-Rha) have been the most widely used, and, although they cause fibroid regression, they can only be used on short term, as temporizing measures in the perimenopausal women, or pre-operatively, to reduce fibroid size, influence the type of surgery, restore haemoglobin levels and apparently reduce blood loss at operation. Surgical and radiological approaches remain the mainstay effective therapies.*

Keywords: *leiomyoma, uterine fibroids, progesterone/ oestrogen receptor modulators*

Rezumat: *Pornind de la observaţia ca fibromiomul uterin este o tumora benigna a tractului genital feminin, dependenta hormonal, terapia medicamentoasa cu agenţi hormonali constituie o alternativa avantajoasa la tehnicile chirurgicale clasice. Analogii Gn-Rh au fost cel mai des utilizaţi, deşi produc o regresie a fibromiomului ei pot fi utilizaţi doar pentru o scurtă perioadă de timp pentru: diminuarea riscului de sângerare intraoperator, prevenirea anemiei si alegerea tipului de intervenţie chirurgicala. Deşi au efecte notabile asupra reducerii volumului fibromului, administrarea lor este însoţită şi de o serie de efecte adverse .*

Cuvinte cheie: *fibromiom uterin, hormoni, modulatori ai receptorilor estrogenici şi progesteronici*

INTRODUCTION

The uterine fibrosis is the most frequent benign tumour of the female genital tract. They are symptomatic in 50% of the cases and have a maximum occurrence at the age between 30 and 40 years.

The medicinal therapy offers a chance to women diagnosed with uterine fibrosis to have an alternative to surgery (Myomectomy, hysterectomy), to procedures of arterial embolization.

Indications of the medicinal therapy

At the present, the therapy with medicine is used only for a short period due to adverse reactions, in the following cases:

- -symptomatically for women in the pre-menopausal phase or for patients which cannot undergo surgery due to the associated pathology
- -preoperatory-reduction of the dimensions of rthe fibroid, reduction of the bleeding and amelioration of the anemia. The possibility of vaginal surgery after the reduction of the dimensions of the fibroid.
- in research

Available medicinal agents

Up to today the most used are theagonists Gn-Rh alone or associated with the adjutant therapy.

The selective modulators of the estrogen receptors (SERMs), the blockers of the progesterone receptors (RU486), the inhibit ants of the aromatase, carbegoline, danazol and gestrinone are the agents that are also used in diverse studies.

The ideal medicine should cause the involution of the fibrosis and should not interfere with the ovulation and the rhythmic of the menstruation.

Analogs Gn-Rh

Gn-Rh and the analogues Gn-Rh have been used on a large scale from 1970. There exist over 2000 analogues Gn-Rh with agonist and antagonist activity and they have been used in diverse situations when the temporary and reversible suppression of the gonadic trophical secretion has been needed. They have been used in endometriosis, hirsutism, premenstrual syndrome and in the FIV protocols.

Action mechanisms

Gn-Rh is a dicapeptide, a produced and freed in a pulsation manner by the hypothalamus **(**the arcuate nucleus and pre-optical nucleus). It reaches the portal system of the hypophysis, and stimulates the FSH and LH synthesis. The biological activity of Gn-Rh is very short; the hormone has a biological division time of 2-4 minutes. The degradation takes place under the influence of the specific peptidases which activity is adjusted by the steroid hormones and LH.

The Gn-Rh agonists have a greater power and longer division time than the natural hormone (Gn-Rh). The potent power and the action time is determined by the substitution of an amino acid, thus, the substitution of an amino acid in the position 6 or 10 leads to the creation of an analogue with an agonist effect, while the substitution in the position 2 or 3 leads to the creation of an analogue with antagonist effect.

Doses and means of administration of the Gn-Rh

- Busereline - subcutaneous 200 μg/day

- Nasal 300 μg/4/day
- Decapeptyl
  - intramuscular 3 mg/month
- Goserelin
  - subcutaneous 3.6 mg/month
- Histerelin
  - subcutaneous 100 μg/day
- Leuprolide
  - subcutaneous 500-1000 μg/day
  - Nasal 400 μg 4/day
  - Intramuscular 3.75-7.5 mg/month
- Naferelin
  - nasal 200 μg 2/day
  - Intramuscular 3 mh/month
- Tryptorelin
  - intramuscular 2-4 mg/month

The central action mechanism of the reduction of the uterine fibrosis is the reduction of estrogen level (effectors of the tumour growth).

Use of Gn-Rh as sole therapy

All studies have shown that the Gn-Rh analogues reduce the volume of the uterine fibrosis, as compared to the placebo or treatment groups. 2 major adverse reactions have been discovered: the reduction of the bone density and symptoms of pseudo-menopause (related to the reduction of the estrogen level), for which the use period of Gn-Rh is restricted to 6 months.

The use of Gn-Rh associated with the adjutant therapy

The efforts to reduce the adverse affects if the therapy with Gn-Rh heva led to the adjuvant therapy (tibolone, ralixofene, progesterone, estrogen, estro-progesterone), it have been a long debate whether the adjuvant therapy reduces or not the benefices of the Gn-Rh. The main target of the adjuvant therapy is to ameliorate the menopause symptoms and reduce the bone demineralization.

Tibolone

The therapy using Tibolone as adjuvant therapy in a series of clinical trials has led to the reduction of the vasomotoric symptoms and to the prevention of the bone demineralization, without compromising the therapeutic efficiency of Gn-Rh (2.5mg/day).

Raloxifene

In a clinical study, acetate Leuprolid (3.75 mg at 28 days) has been administered and raloxifene 60 mg/day for 18 cycles, with no resulting modification of the bone density or of the biochemical markers of the bone metabolism. A striking reduction of the fibrosis dimension has been observed after 6 months.

Progesterone

Medroxiprogesterone acetate can be useful in association with analogues Gn-Rh regarding the secondary effects and the prolonging of the response to the therapy. There is no evidence that the administration of MPS prevents the growing of the fibrosis after the Therapy with Gn-Rh has been finished.

Estrogens

Estrogens are not administered on a routinely basis because of the risk of endometrial hyperplasia.

Estroprogestative therapy

A randomized trial compares 2 groups: the patients of the first group have received GN-Rh with estroprogestative, the second group has received Gn-Rh associated only with progesterone. No significant differences between the two groups have been observed, regarding the amelioration of the menopause symptoms and the reduction of the volume of the fibrosis.

Gn-Rh antagonists

The Gn-Rh antagonists approved by FDA are abarelix (Plenaxix), cetrorelix (Cetriode) and ganirelix (Antagon). These agents are used in injectable form in doses of 5 mg/2x day during the first 2 days, after which 0.8 mg/2x day for at least 3 months.

The Gn-Rh antagonists are directly related to the receptors of the hypophyse for Gn-Rh, The antagonists immediately suppress the synthesis if the hormones of the hypophyse (FSH and LH). The interruption of the therapy with antagonists leads to a quick and predictable recuperation of the secretor function of the hypophyse. There are no randomized clinic trials for the use of antagonists at patients with uterine fibrosis yet, but experimental studies show positive effects at these patients.

Obstructionist of the estrogenic receptors (SERMs)

These agents are most frequently used in the prevention and therapy of mammary cancer with present estrogenic receptors (Tamoxifen, Raloxifen). Any molecule which obstructs the activity of estrogens has a potential effect in the involution of fibrosis. There are no randomized clinic trials for the use of Taximofen at patients with uterine fibrosis yet (endometrial hyperplasia, increase of the fibrosis volume as secondary effects).

Aromatase inhibitors

The Aromatase inhibitors reduce the estrogen levels at women in post-menopause by the inactivation of the transformation of the androstendione in estrogens.

Japanese researchers have used an Aromatase inhibitor (fadrozole) for the reduction of the volume of a complicated fibrosis with urinary retention. After 8 weeks of therapy, the volume of the fibrosis was reduced with 71%. Different from tamosifen, the Aromatase inhibitors do not increase the incidence of endometrial cancer or the risk of thromboembolism.

Antiprogesteronics

The role of estrogens in the increase of the fibrosis volume is well knows, but recent studies have suggested the progesterone plays a role too in the proliferation of the fibrosis.

A dose of 5 mg/day (Mifepristone) may be efficient in the therapy of fibrosis, with few secondary effects. A randomized double bind study made for a period of 6 months with women with fibrosis has proven that the quality of live has become better and that the anemia has become less and that the uterine fibrosis has decreased in volume.

Asoprisnil (SERM)

Has a mixed activity: agonist-antagonist- has a

high tissues selectivity and binds to progesteronic receptors. In the initial phase (I), studies have proven that SERM induces a reversible suppression of the menstruation with favorable effects on the ovulation. In the second phase (II), studies have indicated that this reduces the volume of the fibrosis and the volume of the uterus depending on the dose.

Carbegoline

Is a dopaminergic agonist used in the therapy of the prolactinomes and in ablactation. The theoretical basis for the use in the therapy of uterine fibrosis is the inhibition of the secretion Gn-Rh.

Danazol

Danazol is a synthetic steroid with androgenic effects. Danazol is administered in doses of 100-400 mg/day for 4-6 months, the short- term therapy leading to the reduction of the uterus volume up to 30% and of the fibrosis volume up to 37%. As secondary effects are known: gaining weight, vaginal bleedings, acne, leg edemas.

Gestrinone

Is a steroid with antiestrogenical and antiprogestreonical action at endometrial receptors and other tissue level. It also has an inhibitive effect at the level of the hypophyse inhibiting the FSH and LH synthesis starting from the first month of therapy. Other activity is the modification of the uterine vascularisation. Secondary effects are gaining weight, acne, hirsutism.

Non-hormonal therapy

A series of substances are still being evaluated, they are active by inhibiting the proliferation of the fibroid cells, by diminishing the production of the growth factors, by diminishing the collagen production of by increasing the process of apoptose (programmed death of the cells) – antifibrotic agents (Pifrenidone, Heparine, Interferon- α).

IFN α is a anti- angiogenic cytokine with inhibitive effect on the proliferation of fibromatioc cells in cell cultures. Heparine inhibits the proliferation of the myometrial cells and of the leiomyomatisic cells in vitro . Pirfenidone inhibits the DNA synthesis of the myometric cells and of the leiomyomatisic cell.

CONCLUSIONS

- -We underline the fact that for the majority of women with a reproductive age with uterine fibrosis there is no efficient medicine therapy
- -The analogs Gn-Rh are used on a large scale in the gynecological pathology. As well, the increase in volume of the fibrosis after the interruption of the therapy and the high cost show that the analogs Gn-Rh cannot be used as a sole therapy. The bone demineralization and menopause symptoms are other secondary effects.
- -Aromatase inhibitors and SERMs may be useful for patients in a postmenopausal phase with uterine fibrosis but have no positive effects for patients with fibrosis in a premenopause phase.
- -Mifepristone and anisoprisnil need further rigorous studies and may be efficient in increasing the live quality and reduction of the uterine fibrosis volume.

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