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EDITORIAL

The value of gonadotropin-releasing hormone-agonists together with other drugs for medical treatment and prevention

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Introduction

Gonadotropin-releasing hormone (GnRH)-agonists as analogs of the natural GnRH have gained great importance in gynecological endocrinology and have proven to be particularly useful in clinic and practice being applied to treat a large range of clinical conditions. However, the clinical use is negatively influenced by GnRH-agonist-induced side effects due to hypoestrogenism, which is the main type of action to be used for treatment and prevention.

Besides a high incidence of climacteric symptoms there is manifestation of estrogen depriviation at the tissue level, such as loss of bone density. To avoid this, the combined treatment of GnRH-agonists and other drugs have been studied and up to now various forms of combination that have been proven to be of clinical value not only dealing efficiently with the underlying disease or abnormality to be treated but also re-establish quality of life by elimination of the GnRH-agonist-induced symptoms, such as hot flushes, sweating, sleeplessness, etc. [1].

Purpose and indications for combined treatment are four-fold:

1. Avoiding side effects of GnRH-agonists, such as climacteric symptoms.
2. Improving treatment effectivity.
3. Prolonging treatment effects and reducing re-currence of treated lesions.
4. Upgrading disease prevention.

GnRH-agonists and add-back

One of the most widely used combination concepts is the addition of various drugs, which minimize the side effects without jeopardizing the treatment aim of the GnRH-agonist. This is particularly useful in clinical conditions, where long-term treatment schedules are indicated such as in endometriosis, myoma, etc.

Some of the more commonly used combinations are:

1. GnRH-agonist and progestogens.
2. GnRH-agonist and estrogen/progestogen combinations.

Less commonly used combinations are:

1. GnRH-agonist and tibolone.
2. GnRH-agonist and danazol.
3. GnRH-agonist and biphosphonate.

GnRH-agonists and add-back in women with endometriosis

Principally, treatment is started with the GnRH-agonist and after 3 months the add-back medication is added and both together continued depending on the clinical situation and the patients' adherence.

The clinical usefulness has been shown for the combination of GnRH-agonist and progestogens as well as for the combination of GnRH-agonist and estrogen/progestogen combinations [2–4], alleviating the GnRH-agonist-induced symptoms and preventing tissue and organ integrity, such as avoidance of bone density loss.

A new approach for treatment of endometriosis is the combination of GnRH-agonist and aromatase inhibitors. This type of treatment is directed towards optimizing the therapeutic effect on the endometriotic lesions and not in regard of symptom control caused by the medication [5,6].

This can be particularly indicated in severe pain associated with endometriosis and lesions, which do not regress with GnRH-agonists alone.

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GnRH-agonists and add-back for treatment of myoma

GnRH-agonists in combination with tibolone have been shown to be effective in three ways [7]:

1. Significant reduction in uterine and myoma volume.
2. No significant change in bone turnover.
3. Only a low number of hot flushes.

For myoma treatment also the combination of GnRH-agonists and progestogens has been used starting the progestogens 3 months after the beginning of the GnRH-agonist therapy. The myoma size can be maintained, whereas symptoms are controlled [7]. Also a combination of GnRH-agonist and raloxifene was successfully implemented with a significant decrease of myoma size ($p < 0.05$) in a randomized, placebo-controlled prospective study [8].

Additional indications for combination therapy with GnRH-agonists and tibolone

This type of combination was shown to be effective when used over a longer period of time for severe premenstrual syndrome [9]. Also in resistant menstrual cycle-related irritable bowel syndrome this type of combination therapy was effective by:

1. Significant cure rate ($p < 0.05$).
2. Significant symptom improvement ($p < 0.05$).
3. Significant improvement of quality of life ($p < 0.05$).
4. Prevention of bone loss [10].

Combination of GnRH-agonists and other medications in women with endometrial hyperplasia

GnRH-agonists combined with either medroxyprogesterone acetate (MPA) or tibolone resulted in a regression of the endometrial hyperplasia. The bone density remained unchanged but symptoms were alleviated [11,12].

Oncological aspects of GnRH-agonists and other medications

An add-back type co-treatment with a low-dose estrogen/testosterone and intermittent MPA leads to a significant reduction in mammographic density ($p < 0.02$), a risk factor for breast cancer [13]. Breast cancer risk reduction was also achieved with the combination of GnRH-agonist and tamoxifene or ibandronate [14].

In women with established breast cancer co-treatment of GnRH-agonist with tamoxifene and aromatase inhibitors elicits additional therapeutic effects regarding an event free survival and overall survival [15–17].

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