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REVIEW

GnRH Antagonists : an Update

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ABSTRACT

Gonadotropin releasing hormone (GnRH) antagonists result from multiple amino acid substitutions in the native GnRH molecule. Therefore, they are capable of immediate inhibition of pituitary gonadotropin secretion by competing with the stimulatory effect of GnRH. GnRH antagonists are likely to offer several advantages over the currently available GnRH agonists, such as the absence of an initial gonadotropin stimulation (flare) and the dose proportional efficacy. However, their development was limited by the discovery of side-effects related to their histamine release at the site of injection or even a systemic reaction. After development of GnRH antagonists for twenty years, very effective and safe GnRH antagonists such as Cetrorelix or Ganirelix have been introduced into protocols for controlled ovarian hyperstimulation (COH) to avoid premature luteinizations and are now available for assisted reproduction programs in some countries in Europe and USA. GnRH antagonists have several advantages when compared GnRH agonists due to their different pharmacological mode of action. Further development of GnRH antagonists and their delivery systems will open a broad field of clinical applications.

Key words : gonadotropin releasing hormone (GnRH), GnRH antagonists, controlled ovarian hyperstimulation (COH), cetrorelix, ganirelix

Gonadotropin-releasing hormone

Gonadotropin-releasing hormone (GnRH) plays the central regulatory role in the hypothalamic-pituitary-gonadal axis. It is synthesized and released in a pulsatile manner by the arcuate nucleus in the mediobasal portion of the hypothalamus and acts on the GnRH receptor of the pituitary gland via the hypothalamic hypophyseal portal system. This results in synthesis and release of the two gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Binding of the gonadotropins to their specific gonadal receptors initiates and maintains sexual maturity. GnRH has a half-life of 2-5 minutes and undergoes rapid enzymatic degradation by peptidases. Pulsatile signaling is important for normal gonadal function.

GnRH is a peptide composed of 10 amino acids with crucial functions at positions 1, 2, 3, 6 and 10. Position 6 is involved in enzymatic cleavage, positions 2 and 3 in gonadotropin release, and positions 1, 6 and 10 are important for the three-dimensional structure. Modification of these amino acids at the specific positions can change the stability and binding affinity dramatically (Figure 1).

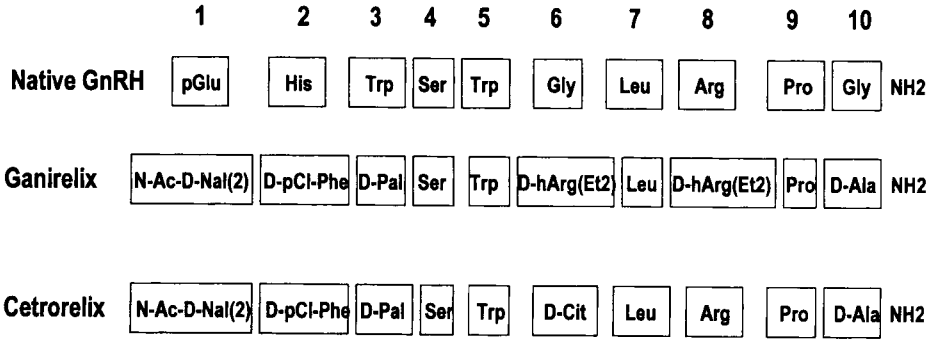

Fig. 1. Amino acid sequences of native GnRH and third-generation GnRH antagonist (Cetrorelix and Ganirelix).

GnRH agonists

Modification of the amino acid structure of GnRH at positions 6 and 10 result in GnRH agonists with increased potency and stability. Some GnRH agonists have a binding affinity for GnRH receptors 100-200 times higher than the native molecule.[1]

This causes a down-regulation of GnRH receptors and suppression of gonadotropins and gonadal function.[2] However, before down-regulation is achieved GnRH agonists cause an initial stimulation of gonadotropins (the so-called 'flare up') and sex hormones lasting for up to 2 weeks. When the treatment is stopped, resumption of pituitary gonadotropin secretion usually begins within two weeks, while full restoration of ovarian function takes place in about 6 weeks. Currently, GnRH agonists can be administered by daily subcutaneous injection, nasal spray or formulated as depot preparations for monthly injections.[3]

GnRH antagonists

GnRH antagonists result from multiple amino acid substitutions in the native GnRH molecule. Due to amino acid modifications in positions 1, 2 or 3, GnRH antagonists bind to the GnRH receptor in the pituitary without inducing signal transduction. Therefore, GnRH antagonists competitively block the action of native GnRH in the pituitary gland. In contrast to GnRH agonists, suppression of gonadotropins occurs within a few hours.

With the first generation of GnRH antagonists, allergic side effects due to induced histamine release hampered the clinical development of these compounds.[4]

These histamine-related side-effects seem to be typical for GnRH antagonists with D-arginine in position 6. Second generation GnRH antagonist, Nal-Glu, was developed by modifying of the amino acid sequence in positions 5 and 6. However, local histamine related side-effects (erythema, edema, induration) were still observed. The introduction of further amino acid modifications at positions 1, 2, 3, 6 and 10 produced GnRH antagonists of the latest generation with higher potency, longer duration of action and no systemic and only minor local side effects[5-10](Figure 1). Of the new GnRH antagonists, Cetrorelix and Ganirelix seem to be the most advanced in clinical development. Clinical applications include controlled ovarian hyperstimulation (COH), the treatment of sex-steroid dependent diseases, and other clinical conditions (Table 1). Recently, both drugs have entered large scale multicenter trials in assisted

reproduction programs and are available for clinical use in some countries in Europe and USA.

Table 1. Potential clinical applications of GnRH antagonists[11,12]

A. Potential short-term treatment indications (1-6 weeks)
   - Prevention of LH surges in controlled ovarian superovulation for assisted reproductive techniques
   - Suppression of excess LH secretion in women with polycystic ovarian syndrome to decrease the incidence of spontaneous abortion
   - Short-term reduction of the volume of leiomyomas prior to surgery or to avoid blood transfusion
   - Immediate interruption of menometrorrhagia
   - Male contraception
   - Protection of the gonads against the toxicity of chemotherapies
   - Diagnostic test of the origin of hyperandrogenism due to an ovarian or adrenal tumor
   - Assessment of GnRH secretion (indirect evaluation of GnRH secretion based on the measurement of the degree of LH suppression)
   - Treatment of threatening ovarian hyperstimulation syndrome (OHSS)
   - Interval treatment of endometrial cancer between diagnosis of and surgery.

B. Long-term indications of GnRH antagonists (several months to many years)
   - Prostate cancer
   - Breast cancer
   - Benign prostatic hypertrophy
   - Precocious puberty
   - Endometriosis
   - Excess ovarian androgen production (polycystic ovaries)

Clinical applications of GnRH antagonists

Controlled ovarian hyperstimulation (COH)

The LH surge plays an important role in reproduction by allowing the resumption of meiosis, the luteinization of the follicular wall and finally in triggering follicular rupture. The LH surge occurs at midcycle under the influence of estradiol.[13] Recent studies support the concept that endogenous GnRH is needed for the estradiol-induced LH surge. In women, the administration of GnRH antagonists prevents the surge, and interrupts the surge if it has already started.[14] This suggests that GnRH is necessary for the LH surge.

The ideal controlled ovarian hyperstimulation (COH) for invitro fertilization and embryo transfer (IVF-ET) requires the absence of a premature LH surge, a factor of cycle cancellation. GnRH agonists are widely used in COH to prevent the premature increase in plasma LH and progesterone levels reported in as many as 25% of patients. However, GnRH agonists have several drawbacks: they requires a period of one to three weeks for the desensitization; their use is associated with the need for high doses of human menopausal gonadotropin (hMG) thus increasing the risk of ovarian hyperstimulation syndrome (OHSS).

The inhibition of a premature LH surge during COH in assisted reproduction is the most developed clinical application of GnRH antagonists.[7,8] GnRH antagonists are competitive inhibitors of GnRH receptors. Their administration rapidly decreases gonadotropin secretion, delays LH surges, and prevents premature ovulation and luteinization in COH.

A dose-dependent suppression of FSH, LH and estradiol concentrations was observed during treatment.[15] Due to the immediate effect of the GnRH antagonists, the premature LH-surge with its negative impact on treatment outcome in assisted reproduction techniques can be prevented by

1. ***Multiple dose protocol*** : Daily subcutaneous administration of Ganirelix or Cetrorelix from stimulation day 5 or 6 onwards until ovulation (0.25mg Ganirelix or Cetrorelix/day) (Figure 2A).

In recent studies, a daily dose of 0.25 mg Ganirelix[16,17]or Cetrorelix[18] prevented LH surges during ovarian stimulation and resulted in a good clinical outcome. Corpus luteum function seemed to be impaired in cycles that were stimulated with hMG

and the GnRH antagonist.[19] However, this impairment was found to be less than GnRH agonist treatment.[20] This protocol did not have any impact on the luteal phase when hormonal support was given.[21]

2. ***Single dose protocol :*** Single subcutaneous administration of Cetrorelix on stimulation day 7 (3mg Cetrorelix) (Fig. 2B).

Recently, single dose Cetrorelix administration was used to prevent premature LH surge in natural cycle IVF[22] and COH[23-25] with no complications and risks of current controlled ovarian hyperstimulation protocols. An acceptable success rate was achieved.

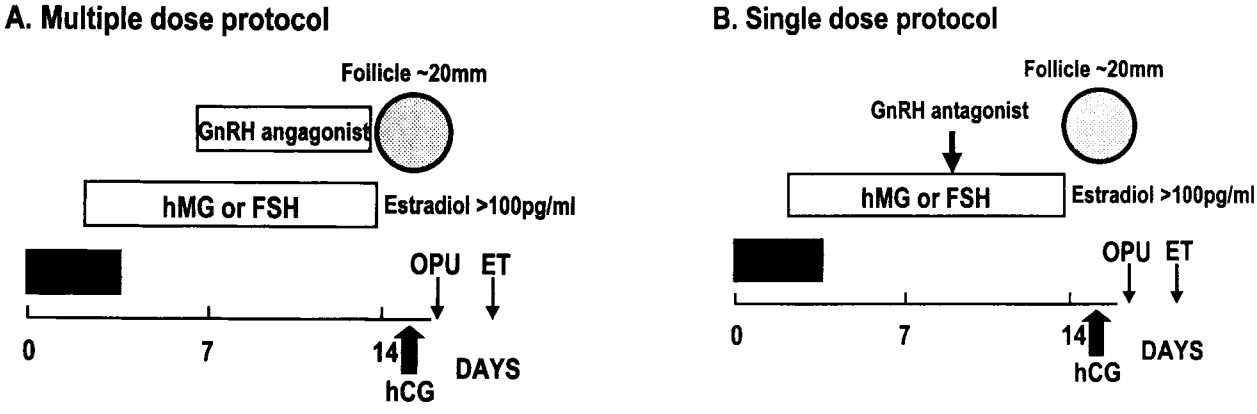

Fig. 2. Controlled ovarian hyperstimulation with hMG/FSH and GnRH antagonists :
A. Multiple dose protocol B. Single dose protocol
(OPU : Oocyte pick-up, ET : Embryo transfer)

Stimulation starts at cycle day 2 or 3 of the spontaneous cycle. As a consequence treatment time can be significantly shortened by both protocols, lowering the number of injections necessary for a successful ovarian stimulation. GnRH antagonists enable the simplification of IVF stimulation, preventing a premature LH surge and possibly allow a better response as compared with GnRH agonists which induce ovarian hyporesponsiveness. The use of GnRH antagonists allows the flexible regimens of ovarian superovulation using fewer doses of hMG, clomiphene citrate/hMG regimens, and eventually the use of assisted reproductive techniques in non-stimulated cycles. Such low dose gonadotropin regimens are important for the reduction of the risk of ovarian hyperstimulation and its consequences.[26-29] In patients undergoing COH, the treatment with GnRH antagonists proved to be an effective and safe new therapeutic principle. No adverse effects on pregnancy course, deliveries or babies were reported.[18,21]

In conclusion, all data obtained to date suggest that the premature LH surge during COH can be easily and effectively prevented by a single or dual injection of GnRH antagonist at higher dosage (3 mg Cetrorelix) in the late follicular phase, or in a multiple application fashion, starting with the minimal effective dose (0.25 mg Cetrorelix or Ganirelix/day) around day 7. GnRH antagonists have several advantages when compared with GnRH agonists due to their different pharmacological mode of action. These advantages, principally immediate suppressive effect and preserved pituitary response, may open new paths to easier approach to ovarian stimulation.

Other clinical applications of GnRH antagonists

Potential long-term treatment indications require a sustained release GnRH antagonist depot

preparation. Recently, the first GnRH antagonist depot preparation, Cetrorelix pamoate, was tested in humans. After an initial loading dose period, a single intramuscular injection of Cetrorelix pamoate can suppress gonadtropins and sex hormones for 3 weeks.[30] Further development of GnRH antagonists and their delivery systems will open a broad field of clinical applications for GnRH antagonists. Recently, clinical applications of GnRH antagonists on benign prostate hyperplasia and leiomyoma uteri were investigated.

Benign prostate hyperplasia

In patients with symptomatic BPH, treatment with cetrorelix is safe and produces long term improvement.[31]

Leiomyoma uteri

In early study, the maximum decrease of the volume of the myomas was reached at the end of 4 weeks' treatment with the second generation GnRH antagonist (Nal-Glu).[32] Subsequent study support the good efficacy of the GnRH antagonist (Cetrorelix) in the medical management of uterine leiomyomas but it required multiple injections.[33] Recently, a depot preparation of the third-generation GnRH antagonist (Cetrorelix) was used for preoperative treatment in twenty premenopausal patients with symptomatic uterine fibroids who were to undergo surgery. The advantages of GnRH antagonist treatment in this indication consist in the short treatment time with a fast restoration of the ovarian function. The avoidance of any initial flare-up in gonadotrophin secretion may explain this extremely fast reduction in fibroid size.[34]

In conclusion, GnRH antagonists are valuable pharmacologic tools for controlled ovarian hyperstimulation and the therapy of sex steroid-dependent diseases. Further development of GnRH antagonists and their delivery systems will open a broad field of clinical applications for GnRH antagonists. Suitable sustained delivery systems and GnRH antagonists with sufficient oral bioavailability represent the present and future of these important compounds.

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