Gonadotropin-releasing hormone analogs: Understanding advantages and limitations

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ABSTRACT

Pituitary stimulation with pulsatile gonadotropin-releasing hormone (GnRH) analogs induces both follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Pituitary gonadotropin secretions are blocked upon desensitization when a continuous GnRH stimulus is provided by means of an agonist or when the pituitary receptors are occupied with a competitive antagonist. GnRH antagonists were not available originally; therefore, prolonged daily injections of agonist with its desensitizing effect were used. Today, single- and multiple-dose injectable antagonists are also available to block the LH surge and thus to cause desensitization. This review provides an overview of the use of GnRH analogs which is potent therapeutic agents that are considerably useful in a variety of clinical indications from the past to the future with some limitations. These indications include management of endometriosis, uterine leiomyomas, hirsutism, dysfunctional uterine bleeding, premenstrual syndrome, assisted reproduction, and some hormone-dependent tumours, other than ovulation induction.

KEY WORDS: Advantages, gonadotropin-releasing hormone analog, limitations

INTRODUCTION

Gonadotropin-releasing hormone (GnRH) and its analogs have been extensively used in clinical medicine since they were identified and synthesized in 1971. This was a logical consequence of the discovery of the amino acid sequence of GnRH, which led to the development of agonistic and antagonistic analogs with many scientific clinical perspectives. Native GnRH stimulates gonadotrophs of the anterior pituitary and has been used for induction of ovulation. The GnRH agonists are more potent and have got a longer half-life than native GnRH. They produce an initial stimulation of pituitary gonadotrophs that results in secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and the expected gonadal response. This response is followed by down-regulation and inhibition of the pituitary-gonadal axis. As compared to GnRH agonists, GnRH antagonists promptly suppress pituitary gonadotropin by GnRH-receptor competition, thereby avoiding the initial stimulatory phase of the agonists. Discontinuation of GnRH antagonist treatment leads to a rapid and predictable recovery of the pituitary-gonadal axis. Agonists would be used as strong sustained stimulators of gonadotropin secretion and the antagonists promised to be a potential tool for chemical hypophysectomy. It was relatively simple to develop safe agonist by just changing one or two amino acids but it required almost 30 years of trial and error with replacement of three or more amino acids to obtain an antagonist with an acceptable pharmacokinetic, safety, and commercial profile.

Half-life of GnRH is 2-4 min as it is degraded by peptidase and cleared by glomerular filtration. This was the sole reason that of GnRH, analogs with agonistic or antagonistic properties have been synthesized to increase their potency and duration. These properties were developed by deleting, substituting

or modifying amino acid sequence at different positions of GnRH.

Gonadotropin-releasing hormone and its analogs are being used therapeutically in many clinical conditions.

OVARIAN STIMULATION

As discussed earlier pulsatile administration of GnRH in physiologic amounts at a frequency that is similar to the endogenous release stimulates the ovaries which will induce ovulation in anovulatory conditions, such as hypothalamic amenorrhea and polycystic ovarian disease.[1]

Gonadotropin-releasing hormone agonists in combination with gonadotropins for ovarian stimulation in assisted reproductive technology (ART) have been extensively investigated. The above combination also termed as "Superovulation therapy" is very effective in women who respond poorly to gonadotropin stimulation or who have premature ovulation. Benefits of this therapy seem to be suppression of endogenous gonadotropin release, prevention of premature ovulation, recovery of a larger number of oocytes, a decrease in the number of canceled cycles, and an increase in pregnancy rate. Now, GnRH antagonists also have been used during the late follicular phase of normal menstrual cycles as well as gonadotropin-stimulated cycles.[2]

TREATMENT REGIMENS

There are many treatment schedules in which GnRH agonists in ART. Their duration and initiation particularly in ovarian hyperstimulation *in vitro* fertilization (IVF)/ intracytoplasmic sperm injection treatments varies. One can start the treatment either in the early follicular or midluteal phase of the preceding cycle. This cycle may be spontaneous or may be under the influence of progestagens and/or estrogens.

Long or desensitization protocol

The idea is to suppress LH hormone so that there is no sudden rise of the same. In this type of protocol the agonist starts in the early, mid-, or late luteal phase in the preceding cycle or the follicular phase until human chorionic gonadotropin (hCG) administration. However, starting in the early luteal phase showed lesser number of eggs retrieved compared to the follicular phase start.[3] More of the dosages of Gonadotropin were needed in the long protocol compared to the other regeems like ultrashort, short and higher number of eggs were obtained as shown in a meta analysis[4] when compared to the long follicular phase protocol more profound and prompt suppression was found after midluteal administration.[5]

Among many advantages one of the major advantages of the long protocol of GnRH agonist administration is that the initiation of exogenous gonadotropins after pituitary desensitization can be delayed to prevent ovum pickup (OPU) in the weekends (the so-called "programming"), without any detrimental effect on IVF outcome.[6] Furthermore, delay in hCG administration for 24-48 h seemed to improve fecundity and contributes to planning of the OPU.[7,8] Ideally the GnRH agonist should be started one week before the expected menses. There is an initial flare up of the FSH and LH but this seems to lasting for a short time. Later the receptors are downloaded in the pituitary to a very low level. Except PCOS , all other women the dose can be halved when the menses starts and Gonadotropins can be stated for stimulation of the follicles. This kind of half the dose continuation along with gonadotropins keeps the LH at a low levels rather than getting the surges.[9] The agonist is given on the day of hCG also.The agonist depletes the receptor, which regenerates only long after the agonist administration is stopped. However, sometimes the dose used may be excessive, causing too much of suppression of the ovaries. All this kind of suppression will cause luteal phase defect, which, therefore, needs supplementation.[10] Ovarian hyper stimulation syndrome has to be thought of when high dose is used for ovarian stimulation. Some of the women have a cyst on the second day of menses and this is one of the side effect of starting the GnRH analogue in the luteal phase, which leads to cancellation of the cycle.

Short protocol

Instead of starting the GnRH analogue in the luteal phase of the cycle it can be started at the beginning of the cycle. This leads to the flare effect of FSH and LH and augments the folliculogenesis already in progress. Though follicles are recruited with this method, the excess of LH in the early part may be deleterious to the growing follicle. With this method the dosage of gonadotropins can be reduced for an initial period of 2-3 days at least, wherein the cost would come down. The dose of agonist it is stopped when the follicular maturity is attained and ovulation triggering planned with hCG. This is one of the methods chosen for a poor responder.

Microdose flare protocol

This is not very popular and is very similar to the short protocol except that the dose of agonist is reduced.[11]

Stoping gonadotropin-releasing hormone agonist protocol

In this protocol though the GnRH analogue is started in the luteal phase one week before the expected start of menses, is it stopped at the initiation of gonadotropin therapy since the suppression is less to start the gonadotropins. However this is not popular due to the irratic response.[10,12]

Ultrashort protocol

Gonadotropins are started on the day of the menses and the agonist is also started but stopped in 2-3 days, as the suppression will outlast the stimulation.[13] In general, protocols of short, microdose fl are, preparatory protocol/stop GnRH-a, ultrashort are not popular due to the erratic responses.

ANTAGONIST PROTOCOLS

Unlike GnRH agonists, there is no hypersecretion of gonadotropins but instead cause an immediate and rapid, reversible suppression of gonadotropin secretion. The principal mechanism of action of GnRH antagonists is competitive occupancy of the GnRH-receptor. Here the antagonists are are started half way through the gonadotropin stimulation so that the LH suppression is done and LH surge is prevented.

Single-dose protocol

The Ovarian stimulation is done with gonadtropins starting on day 2 or 3 of the menstrual cycle. The antagonist is given on day 7 as a fi xed protocol (French protocol).[14] Once a single injection is given the LH surge prevention is seen for the next 4 days. In case the patient does not get ready for hCG trigger within this time frame, she is given additional daily doses and including the day of hCG trigger. This protocol is easy to use, well-tolerated with only mild and transient injection site reactions, and ensures patient compliance.

Multiple-dose protocol

The stimulation wth gonadotropins is started on day 2 or 3 of the menstrual cycle. In the fl exible protocol (Ludwing protocol), GnRH antagonist is started once the leading follicle is ≥14 mm.[15] When the multiple-dose protocol is done, it avoids profound LH suppression which causes severe decrease in estradiol levels often seen in single-dose protocol.

Multiple-dose protocol is a simple, safe, and effi cient approach for preventing LH surge. On the other hand, the fl exible protocol avoids unnecessary injections when risk of LH surge is minimal and hence uses less total antagonist ampoules and less gonadotropins. Hence, it appears as a more cost-eff ective approach.[15]

There is a role of agonist as a trigger for ovulation induction instead of hCG to avoid Ovarian hyper stimulation syndrome and can be used in an antagonist cycle or in a intrauterine insemination cycle when the follicle is large.

Precocious puberty

It is a well-known fact that maturation of the pituitary-gonadal system requires pulsatile GnRH stimulation. Idiopathic precocious puberty is the disorder characterized by premature GnRH activity. The aim of various therapeutic methods was to suppress the pituitary gonadal function, in precocious puberty also long-term administration of GnRH agonists has proved remarkably safe and effective.[16,17]

Within 6-18 months of daily treatment with an agonist, pubertal levels and patterns of secretion of gonadotropins and sex hormones revert back to prepubertal levels and patterns. One more beneficial effect of this therapy is the regression of secondary sexual characters and stoppage of menstrual bleeding and as soon as the treatment is discontinued, gonadotropin and steroid genesis resume. After which the child follows the expected clinical progression through normal puberty.

A variety of GnRH agonists have been used to treat precocious puberty In Europe, deslorelin, decapeptyl, triptorelin, and buserelin have been most commonly used. In the United States, nafarelin (800-1800 mcg/day intramuscularly) or leuprolide (4-50 mcg/kg/day subcutaneously) have been found to be effective.[18]

Delayed puberty

Long-term pulsatile administration of GnRH may initiate puberty in both boys and girls with delayed puberty.[17]

Endometriosis

Endometriosis is characterized by presence of ectopic endometrial implants which are subjected to the same cyclical hormonal influences as normal endometrium. Its management by GnRH agonists is based on their ability to produce amenorrhea and anovulation. Initially the therapeutic response characterized by an initial increase in gonadotropins and estradiol followed by sustained hypoestrogenism, amenorrhea, and anovulation. Several controlled and randomized trials have shown that if GnRH agonists are used for the treatment of endometriosis for at least 6 months have shown to induce amenorrhea, anovulation, and regression of endometriosis and its associated clinical symptoms.

Uterine leiomyomata (fibroids)

These are the most common benign tumors of female reproductive tract. Nothing has to be done for asymptomatic ones unless their large size, rapid growth, or degeneration causes symptoms requiring intervention. Prompt action is required when fibroids are associated with menorrhagia or other menstrual disorders. Leiomyomata may also be associated with infertility, and the incidence of spontaneous pregnancy loss seems to be higher in patients who have these tumors. It has been recognized that estrogen is the

trigger factor for the growth of leiomyomata. These tumors regress in hypoestrogenic states, like menopause. The basis for the medical treatment of leiomyomata with GnRH agonists is that they produce profound hypoestrogenic state. The use of GnRH agonists in the treatment of leiomyomata may eliminate the need for surgery in selected cases (i.e. perimenopausal or high-risk surgical) or decrease the surgical risk (e.g. diminished size of remaining fibroid tissue) when surgery is contemplated. Thus, the main goal of the pretreatment with GnRH agonists is to reduce the blood loss during surgery, and the reduced size of the tumor makes operation less complicated. However, the reduction in size following GnRH-a is about 50% and may grow once treatment is stopped. Add-back therapy is not useful in conjunction with GnRH agonists for treatment of women with leiomyomata. Although these women also have the side effects associated with hypoestrogenism, adding hormone replacement therapy (HRT) (estrogen and progesterone) counteracts the desired hypoestrogen effect needed to shrink the tumor.[17]

Hormone-dependent tumors

Some hormone-dependent and malignant tumors of the breast, ovary, and endometrium, are treated with the high doses of GnRH agonists. This causes suppression of gonadotropin secretion.[19,20] This mechanism causes decreased secretion of pituitary gonadotropin and gonadal steroids, resulting in medical castration. These agents have direct effect steroidogenesis of target tissues.

Hirsutism

Hirsutism is caused by excessive androgens by the ovaries or adrenals and increased sensitivity of the hair follicles to normal circulating androgen levels. These hyperandrogenic states in women are frequently associated to polycystic ovarian disease. Suppression of ovarian function with GnRH agonists has been found to be beneficial in hirsute women. With the reduction in hirsutism this therapy also decreases serum levels of gonadotropin, total testosterone, free testosterone, and androstenedione. Some of the clinical trials have evaluated the effectiveness of adding sex hormones to GnRH agonist therapy as add-back therapy have further decreases serum testosterone levels, reduces the hypoestrogenic side effects of analogs, and results in greater reduction of hirsutism.[21]

Dysfunctional uterine bleeding

Dysfunctional uterine bleeding (DUB) is the most common disorder characterized with anovulation or oligo-ovulation in the absence of organic or systemic disease. One of the effective medical managements of DUB associated with abnormal and acyclic bleeding is suppression of the ovarian function with GnRH agonists. Due to the increased expenses, GnRH-a is not popular for DUB. In long-term treatment for DUB, add back therapy with HRT should be supplemented to avoid the side effects related to hypoestrogenism.

Endometrial ablation

The aim of this procedure was to sufficiently eliminate or suppress menstrual flow to avoid the level of anemia requiring a hysterectomy. Endometrial ablation entails destruction of the entire endometrial layer by means of laser, electrocautery, electrosection, or heating, leaving the uterine cavity intact but scarred and devoid of endometrium. To achieve maximum ablation, the endometrium should be as thin as possible at the start of ablative treatment. Because of their hypoestrogenic effects, GnRH agonists in usual doses administered for approximately 8 weeks have been found to be very effective in achieving the desired endometrial thinning before the procedure.[22] Once again, this prolonged use is expensive.

Premenstrual syndrome

It is characterized by irritability, depression, and fatigue accompanied by bloating, breast tenderness, and/or headache during the luteal phase of the cycle. Though it has been reported in 80% of the women in reproductive age group but if strict diagnostic criteria have been used only 5% have suggested.[23] some of the behavioral symptoms seen in premenstrual syndrome (PMS) are labile mood, hypersensitive nature, crying spells, social withdrawal, and difficulty in concentration.

Treatment of PMS with GnRH analogs as long-term treatment has been limited due to hyoestrogenic side effects, loss of bone mineral density and cost. But with the advent of add-back therapy, there has been a resurgence of interest in treating this condition with GnRH analogs. As expected, GnRH agonist treatment markedly alleviated PMS symptoms. The addition of estrogen, medroxyprogesterone acetate, or a combination of these agents was equally effective, whereas placebo treatment alone was associated with some increase in symptoms compared with GnRH agonist therapy alone. However, GnRH-a for PMS is not popular due to the high cost.

Role of GnRH analogue for fertility preservation during chemotherapy

Due to the severe suppression of the follicles in the ovary, GnRH – a can be used to protect the oocytes prior to starting of the chemotherapy. Cochrane review confirms the role of GnRH- a before chemotherapy and suggest that this is given throughout the chemotherapy duration.[24]

SUMMARY

This review is an overview of the use of GnRH analogs which is potent therapeutic agents that are considerably

useful in a variety of clinical indications from the past to the future with some limitations.

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