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Ganirelix

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Contents

Abstract

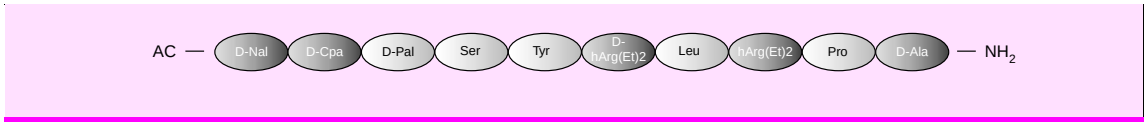
▲ Ganirelix is a synthetic third generation gonadotropin-releasing hormone (GnRH) antagonist that is administered via the subcutaneous route.

▲ The drug competitively blocks GnRH receptors in the anterior pituitary gland, preventing endogenous GnRH from inducing luteinising hormone (LH) and follicle stimulating hormone release.

▲ Ganirelix effectively inhibited LH surges during controlled ovarian stimulation in a large, multicentre clinical trial in women undergoing *in vitro* fertilisation. A vital pregnancy rate per embryo transfer of 40.3% was achieved at weeks 5 to 6 after treatment with the 0.25 mg/day dosage.

▲ Subcutaneous ganirelix has been generally well tolerated in clinical trials. The most common adverse events were local injection site events, asthenia, nausea, malaise, headache and fatigue.

Features and properties of ganirelix (ORG 37462, RS 26306)	
Indications	
Female infertility	Approved
Mechanism of action	
Gonadotropin-releasing hormone (GnRH) antagonist	Blocks GnRH receptors in anterior pituitary, which inhibits the secretion of follicle stimulating hormone and luteinising hormone.
Dosage and administration	
Usual dosage	0.25mg once daily for 5 days
Route of administration	Subcutaneous
Pharmacokinetic profile (*0.25 mg/day*) subcutaneously	
Peak plasma concentration	14.8 μg/L
Time to peak plasma concentration	≈1h
Area under the plasma concentration-time curve	96 μg/L • h
Adverse events	
Most frequent	Local injection site events, asthenia, nausea, malaise, headache, fatigue



Ganirelix

Infertility is a significant problem with up to 10 million women affected in developed countries (reviewed by Prevost[1]). Treatment of infertility, including marked refinements in *in vitro* fertilisation (IVF) techniques, has improved greatly in recent years. During IVF and controlled ovarian stimulation, the ability to inhibit premature surges of endogenous luteinising hormone (LH) is important because elevated LH levels, in the presence of follicular immaturity, may lead to an undesirable early increase in progesterone levels.[2]

Gonadotropin-releasing hormone (GnRH) is a decapeptide produced by the hypothalamus that controls the release of LH and FSH from the anterior pituitary.[3] GnRH agonists have traditionally been used to inhibit the secretion of LH and FSH. This suppression occurs largely as a result of continuous exposure of the pituitary gland to the agonist producing a downregulation of GnRH receptors, desensitising the gland to the effects of endogenous GnRH.[3,4] The suppression is, however, preceded by an initial increase in gonadotropin levels. Treatment with GnRH agonists is started 2 weeks before the IVF cycle in order for adequate pituitary suppression to develop.[2,5] GnRH antagonists exert their effects by competing with endogenous GnRH for access to GnRH receptor binding sites.[4] At sufficient concentrations, the antagonist saturates the binding sites and prevents endogenous GnRH from exerting any effects on the pituitary. This causes an immediate inhibition of gonadotropin secretion without inducing any downregulation of GnRH receptors.[4] Thus, GnRH antagonists would appear to be preferable to agonists for the inhibition of gonadotropin secretion. However, their development has been hampered by low biological potency and a tendency to induce histamine release (reviewed by Lønning[6]).

Ganirelix is a third generation synthetic GnRH antagonist with a low propensity to cause anaphylactoid reactions when compared with earlier generations of antagonists.[7] Ganirelix has the potential to be a useful therapy in many conditions where suppression of endogenous gonadotropins is required. This review concentrates solely on the therapeutic use of ganirelix in female infertility. The drug is also being assessed in the treatment of endometriosis but its role in this context is not discussed in this article. In all trials, unless otherwise stated, ganirelix was administered subcutaneously.

1. Pharmacodynamic Profile

- Ganirelix (0.125, 0.25 and 0.5mg once daily for 7 days) significantly decreased LH, FSH and estradiol levels in 45 healthy premenopausal women. After the last dose, LH, FSH and estradiol were decreased by 74, 32 and 25% compared with baseline in the 0.25mg group. Nadirs were reached in 4 hours for LH and 12 to 16 hours for FSH and estradiol. These levels returned to baseline within 24 hours after the last dose and increased further over the next 24 hours.[8]

2. Pharmacokinetic Profile

- The pharmacokinetic profile of ganirelix, administered by subcutaneous injection,[5] has been investigated in premenopausal women. Additional trials in men[9] and postmenopausal women[10] are not discussed in this article.

- Ganirelix was well absorbed after subcutaneous injection of 0.25mg (n = 15 volunteers), with a mean maximum serum concentration (C_{max}) of 14.8 μg/L at 1.1 hours (t_{max}) and area under concentration versus time curve from zero to infinity ($AUC_{0-\infty}$) of 96 μg/L · h. Absolute bioavailability was 91% and clearance and volume of distribution

(measured after a 0.25mg intravenous dose) were 2.4 L/h and 43.7 L, respectively. Elimination half-life ($t_{½\beta}$) was 12.8 hours.[11]

• Administration of subcutaneous ganirelix 0.125, 0.25 and 0.5mg once daily for 7 days to 3 groups of 15 volunteers resulted in dose-proportional mean C_{max} (5.2, 11.2 and 22.2 μg/L at approximately 1 hour after the last injection) and AUC_{0-24} (33.0, 77.1 and 137.8 μg/L · h) values. Steady-state conditions were reached between day 2 and 3 and trough serum concentrations were 0.31, 0.63 and 1.09 μg/L. Mean $t_{½\beta}$ ranged from 13.7 to 16.3 hours with the 3 doses.[8]

3. Clinical Trials

• Ganirelix prevented premature LH surges in 329 women undergoing IVF during a multicentre, double-blind, dose-finding trial.[12] From day 2 to 6 of the menstrual cycle, each patient received a once daily fixed dose of recombinant FSH. From day 7, the dose of FSH was altered according to the size of the developing ovarian follicles.

• Patients were randomised to receive subcutaneous ganirelix 0.0625mg (n = 31), 0.125mg (n = 65), 0.25mg (n = 69), 0.5mg (n = 69), 1mg (n = 65) or 2mg (n = 30) once daily from day 7 continued up to the day of human chorionic gonadotropin (HCG) administration. HCG was administered when at least 3 follicles greater than 17mm in diameter were seen on transvaginal ultrasound. The median duration of ganirelix therapy was 5 days.

• During the study an external independent advisory committee who reviewed the data indicated that the lowest (0.0625mg) and highest (2mg) dose treatment groups should no longer receive therapy because of LH rises of ≥ 10 IU/L and decreasing estradiol levels with follicular arrest, respectively.[12]

• Ganirelix caused a dose-dependent decrease in serum LH levels. Median levels on the day of HCG administration ranged from 0.4 IU/L for the 2mg group to 3.6 IU/L for the 0.0625mg group (fig. 1). The 0.25mg dose appeared to be the minimal effective dose for preventing LH surges (median 1.7

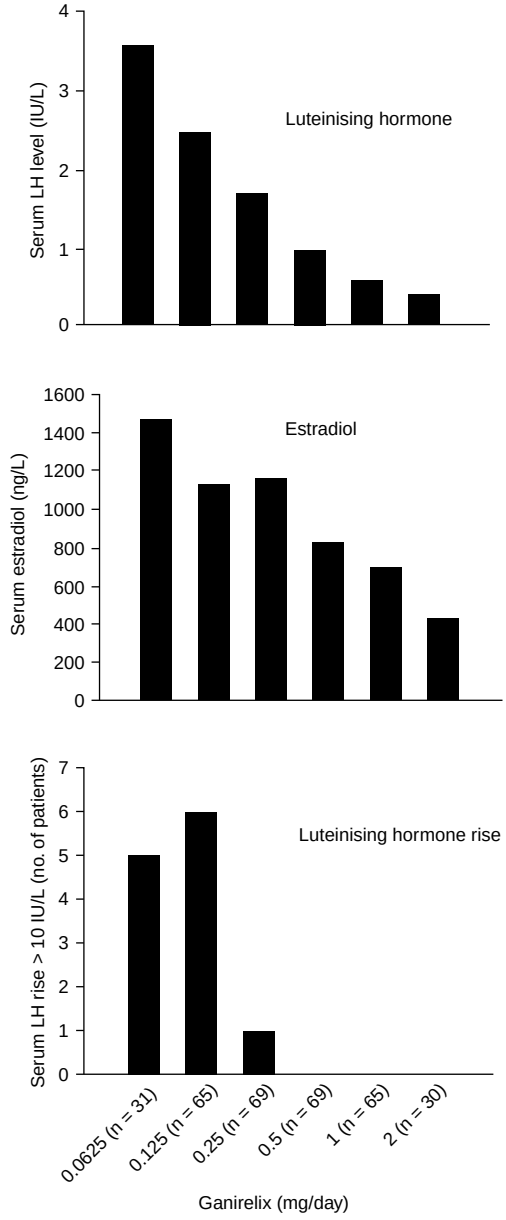


Fig. 1. Effect of subcutaneous ganirelix on serum luteinising hormone (LH) and estradiol levels. Median levels of LH and estradiol on the day of human chorionic gonadotropin (HCG) administration (just before termination of ganirelix therapy) and the number of patients who experienced LH rises >10 IU/L in 329 women undergoing FSH-induced ovarian stimulation as part of an *in vitro* fertilisation (IVF) programme.[12]

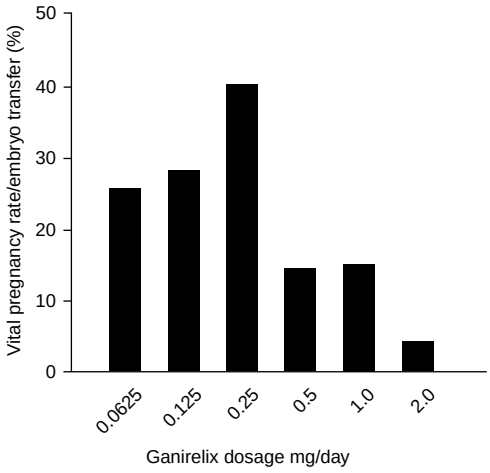


Fig. 2. *In vitro* fertilisation outcome using ganirelix protocol. Vital pregnancy rate after *in vitro* fertilisation in women treated with ganirelix 0.0652mg (n = 31), 0.125mg (65), 0.25mg (69), 0.5mg (65), 1mg (65) or 2mg (30) per day for a median of 5 days to prevent premature luteinising hormone surge during controlled ovarian hyperstimulation with recombinant follicle-stimulating hormone. Ganirelix treatment was stopped and human chorionic gonadotropin was given when at least 3 follicles of ≥17mm diameter were observed and oocyte retrieval was performed 30 to 36 hours afterwards. Luteal phase support was given as per clinics' standard protocol from the day of embryo transfer.[12]

IU/L). 12 patients receiving ganirelix 0.25 [1 of 69 (1.4%)], 0.125 [6 of 65 (9.2%)] or 0.0625mg [5 of 31 (16.1%)] experienced rises in LH levels to >10 IU/L but only one of the rises was severe enough to warrant cancellation of the IVF procedure (fig. 1). A further 3 noncompliant patients also experienced LH surges.[12]

• The rise in estradiol levels, secondary to FSH-induced ovarian stimulation, decreased with ganirelix administration in a dose-dependent manner (the 2mg group actually experienced a slight decrease in estradiol levels after the first ganirelix injection). Median estradiol levels on the day of HCG administration ranged from 430 to 1475 ng/L (fig. 1), with a level of 1160 ng/L for the 0.25mg group.[12]

3.1 Outcome of *In Vitro* Fertilisation

• Follicular growth was comparable in all dosage groups of the dose-finding study. The mean number of good quality embryos was similar in all dosage groups and ranged from 2.5 to 3.8. However, the implantation rate was only 9, 8.8 and 1.5% in the 0.5, 1 and 2mg groups, respectively, compared with 14.2, 16.6 and 21.9% in the 0.0625, 0.125 and 0.25mg groups, respectively. The number of pregnancy losses in the first 6 weeks was also higher in the 1 and 2mg groups. The vital pregnancy rate at 5 to 6 weeks (fig. 2) and ongoing pregnancy rate 12 to 16 weeks from embryo transfer were highest in the ganirelix 0.25 mg/day group (40.3 and 37.1% per transfer).[12]

• A healthy boy and healthy girl (Apgar score 9/10 for both) were delivered by elective Caesarean section at 37 weeks' gestation after a 32-year old patient had received treatment with ganirelix 0.125 mg/day in an IVF protocol.[13]

4. Tolerability

• 20.5% of 333 women who received daily subcutaneous injections of ganirelix (0.0625 to 2mg) for 4 to 5 days reported at least 1 moderate injection site reaction and 1.2% reported a severe local reaction (including skin erythema, swelling, bruising, pain or itching). Erythema of the skin was the predominant symptom initially and was dose-dependent (3.2% of the 0.0625mg *vs* 33% of the 2mg group; 17.1% of the 0.25mg group).[12]

• Adverse events documented as possibly or probably drug-related occurred in 11 patients and included asthenia, nausea and malaise. None of the patients withdrew from this trial because of drug-related adverse events. Eight patients in the trial were hospitalised because of complications related to the IVF procedure, including ectopic pregnancy (n = 3), ovarian hyperstimulation syndrome (n = 2), miscarriage (n = 1), fever (n = 1) and pelvic inflammation (n = 1).[12]

• In a woman who had imminent ovarian hyperstimulation syndrome after ovarian stimulation for IVF (using ganirelix 0.125 mg/day to prevent LH

surge), increasing the dose of ganirelix to 2 mg/day was effective in reducing serum estradiol levels (baseline 22 315 pmol/L) and resolving abdominal discomfort, ovarian enlargement and ascites.[14]

- In 45 healthy premenopausal volunteers who received ganirelix 0.125, 0.25 or 0.5 mg/day for 7 days, the most common adverse events (which were not dose related) were headache (32 volunteers), injection site events (20) and fatigue (11).[8]

5. Ganirelix: Current Status

Ganirelix is a synthetic third generation GnRH antagonist that inhibits LH surges during controlled ovarian stimulation. It markedly decreases endogenous gonadotropin levels without exhibiting significant histamine releasing properties. Ganirelix has been approved for the treatment of female infertility in the USA.

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