Lutropin alfa: a guide to its use in female infertility

Adapted from Drugs 2008; 68 (11): 1529-40[1]

What is the rationale for developing the drug?

Infertility in females is often caused by anovulation.[1] One cause of anovulation may be hypogonadotropic hypogonadism, which is a rare condition characterized by reduced hypothalamic or pituitary activity resulting in abnormally low serum levels of gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), and negligible estrogen activity.[1] These women are amenorrhoeic, have no evidence of endogenous estrogen production, have non-elevated prolactin levels, normal or low FSH levels and no detectable space-occupying lesion.[1] Gonadotropin-releasing hormone (GnRH) agonists have been used off-label to treat hypogonadotropic hypogonadal women with intact pituitary function, as it restores the periodic release of both FSH and LH. Daily injections of gonadotropins are an alternative treatment in patients with pituitary disease or who do not respond adequately to treatment.[1] The off-label use of human menopausal gonadotropin (hMG) [a urinary extract containing FSH and LH] has several limitations as an ovarian stimulant in this patient population, including an inherent variability in LH content, making it difficult to control the LH dose being administered.[1]

There is a need, therefore, for the development of LH formulations with consistent hormone content, thereby providing the possibility of precise control of LH activity in patients who require LH therapy. Lutropin alfa (Luveris®) is the first and only currently available recombinant human form of LH.[1]

Adis Evaluation

Key clinical benefits and limitations of lutropin alfa in stimulating follicular development in infertile hypogonadotropic hypogonadal women

Clinical benefits

Provides consistent hormone content
Promotes optimal follicular development
Generally well tolerated
Allows individual tailoring of the stimulation protocol

Limitations

Definitive effect on pregnancy has not yet been established

How does the drug work?

LH belongs to a family of heterodimeric glycoprotein hormones including FSH, human chorionic gonadotropin (hCG) and thyroid-stimulating hormone, each with a unique β-subunit that confers physiological specificity.[2] LH binds rapidly and reversibly to a receptor that also binds hCG and is expressed on the granulosa and theca cells.[2] In the ovaries, during the follicular phase, LH stimulates the theca cells to produce androgens, which are converted by the granulosa cell aromatase enzyme to estradiol, which, in turn, supports FSH-induced follicular development.[3,4] At mid-cycle, ovulation and corpus luteum formation are triggered by high levels of LH, followed by progesterone production in the corpus luteum.[4] Furthermore, during later stages of follicle development, granulosa cells also express LH receptors and become receptive to LH stimulation.[5] Consequently, LH can influence both the theca and granulosa cells, and exert virtually all the physiological actions of FSH.[5]

Lutropin alfa is a glycoprotein composed of non-covalently bound α- and β-subunits, and has activity similar to that of native LH.[2,6] In terms of stimulating follicular development in anovulatory women who are deficient in LH and FSH, the primary effect of lutropin alfa is to increase the secretion of estradiol by the follicles.[4]

Who should receive the drug?

Subcutaneous lutropin alfa, in combination with a separate subcutaneous injection of recombinant FSH (follitropin alfa; GONAL-f®), is indicated to stimulate follicular development in certain infertile women (table I). Both FSH and LH activity are needed for optimal follicular growth and maturation.[3] In the EU, a combination of lutropin alfa 75 IU and follitropin alfa 150 IU (Pergoveris™),[7] is also approved for the stimulation of follicular development in women with severe LH and FSH deficiency, but a specific discussion of this formulation is beyond the scope of this article.

In hypogonadotropic hypogonadal women, what is its effect …

The efficacy of subcutaneous lutropin alfa in promoting follicular development in hypogonadotropic hypogonadal women (18–40 years of age) has been evaluated in two randomized, multicentre, dose-finding studies,[8,9] a randomized, double-blind, placebo-controlled, multicentre study[10] and its open-label extension,[11] and a

1172-0360/09/0005-001/$19.95

Table I. Prescribing summary of subcutaneous lutropin alfa (Luveris®)[1,4,6] a

Featured indication	
EU:[4] stimulation of follicular development in women with severe luteinizing hormone (LH) and follicle-stimulating hormone deficiency (defined as an endogenous serum LH level <1.2 IU/L in clinical trials) US:[6] stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (<1.2 IU/L)	
Mechanism of action	
Stimulates theca cells to secrete androgens, which are used as substrate by granulosa cell aromatase enzyme to produce estradiol	
Dosage and administration	
Dosage in initial treatment cycle	75 IU once daily (in combination with follitropin alfa 75–150 IU/d as two separate injections)
Monitoring	Ovary ultrasonography and serum estradiol levels
Duration of treatment in each cycle	Should usually not exceed 14 d, unless signs of imminent follicular development are present
If treatment produces optimal response	Administer human chorionic gonadotropin 24–48 h after the last dose (to complete follicular development and effect ovulation in the absence of an endogenous LH surge)
Dosage in subsequent treatment cycles	Individualize based on the response in the preceding cycle
Availability	
Vial containing 75 IU lutropin alfa powder for reconstitution (reconstitute with 1 mL of sterile water for injection [provided])	
Pharmacokinetic profile	
Mean peak serum drug concentration (C_{max})[b]	1.1 IU/L
Median time to C_{max}[b]	6 h
Bioavailability	56% (after a single subcutaneous 10 000 IU dose)
Time to steady state	2 d
Estimated volume of distribution at steady state	8–10 L
Total body clearance	≈2–3 L/h
Mean terminal elimination half-life[b]	≈14 h
Elimination[b]	<5% excreted unchanged in the urine
Profile in special populations	Not yet established in patients with renal or hepatic impairment
Potential drug interactions	
Concomitant follitropin alfa does not affect exposure to lutropin alfa, and vice versa Other drug interaction studies with lutropin alfa have not been conducted	
Contraindications	
EU:[4] ovarian, uterine or mammary carcinoma; active, untreated tumours of the hypothalamus and pituitary gland; ovarian enlargement or cyst not due to polycystic ovarian disease; gynaecological haemorrhages of unknown origin US:[6] primary ovarian failure, uncontrolled thyroid or adrenal dysfunction; an uncontrolled organic intracranial lesion (e.g. pituitary tumour); ovarian enlargement or cyst of undetermined origin; abnormal uterine bleeding of undetermined origin; sex hormone-dependent tumours of the reproductive tract and accessory organs	

a Consult local prescribing information for further details.

b After a single subcutaneous 150 IU dose; the concentration of a 75 IU dose is too small to allow proper quantification.

noncomparative, multicentre trial.[12] Two of the trials are available only as abstracts,[9,10] and additional data for two studies[8,10] have been reported in the US prescribing information.[6] Trial sizes (n = 38–40) are small because of the rarity of the condition.

The primary efficacy endpoint was the proportion of patients with optimal follicular development (defined as at least one follicle with a mean diameter of ≥17[6,8-11] or ≥18[12] mm, plus a mid-luteal progesterone level ≥25–30 nmol/L,[6,8-11] with a preovulatory serum estradiol level ≥400[6,8,10,11] or ≈600[9] pmol/L).

… on follicular development …

Dose-finding studies revealed a significant dose-dependent increase in the rate of optimal follicular development among women with hypogonadotropic hypogonadism and profound LH deficiency (<1.2 IU/L) who received subcutaneous lutropin alfa 0–225 IU/day plus follitropin alfa.[8,9] A lutropin alfa dosage of 75 IU/day (approved dosage) was sufficient for promoting optimal follicular development and steroidogenesis in 46% of treatment cycles.[8]

In the double-blind trial, women receiving lutropin alfa 75 IU/day plus follitropin alfa showed significantly higher

rates of optimal follicular development than the recipients of placebo plus follitropin alfa, regardless of whether excessive follicular development was[6,10] or was not[6] included as success (figure 1).

Rates of ovulation (defined by mid-luteal phase serum progesterone levels ≥25 nmol/L) were 46% with lutropin alfa plus follitropin alfa versus 15% with placebo plus follitropin alfa, mean preovulatory serum estradiol levels were 549 versus 78 pg/mL, and mean endometrial thickness was 7.4 versus 5.0 mm (statistical analysis not reported).[6]

In the extension trial, high rates of follicular development were observed in lutropin alfa plus follitropin alfa recipients. Follicular development was observed in 87.1% of all patients receiving lutropin alfa and follitropin alfa over three cycles of treatment.[11] In patients who had initially received placebo plus follitropin alfa during the lead-in trial, 63.6% showed follicular development when they received lutropin alfa plus follitropin alfa during the extension phase. In contrast, during the initial double-blind phase, one patient (9.1%) receiving placebo plus follitropin alfa achieved follicular development.[11]

A high rate of optimal follicular development in patients receiving lutropin alfa plus follitropin alfa was also seen in the noncomparative trial, with lutropin alfa 75 IU/day being effective in 94% of treatment cycles.[12]

… and pregnancy rates?

In the extension trial, after three cycles of treatment, pregnancy (positive pregnancy test) was achieved in 64.5% and clinical pregnancy in 51.6% of all patients receiving lutropin alfa plus follitropin alfa.[11] In patients who had received placebo plus follitropin alfa during the double-blind lead-in trial, clinical pregnancies in the extension phase occurred in 36.4% of patients after treatment with one cycle of lutropin alfa plus follitropin alfa.[11]

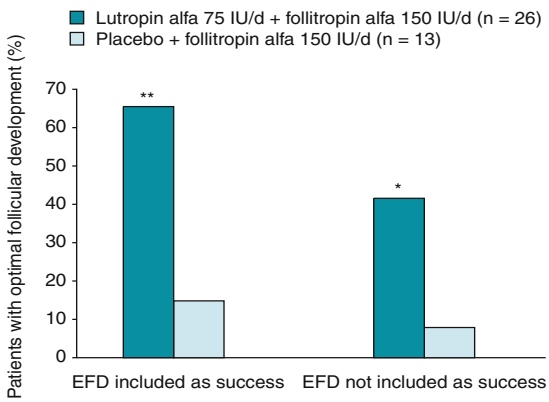

Fig. 1. Efficacy of lutropin alfa in hypogonadotropic hypogonadal women.[6,10] Rate of optimal follicular development after cycle 1 of therapy in a randomized, double-blind trial in women receiving lutropin alfa 75 IU/d or placebo (both coadministered with follitropin alfa 150 IU/d).[6,10] **EFD** = excessive follicular development. * p = 0.034, ** p = 0.006 vs placebo.

In the noncomparative trial, the pregnancy rate per cycle with hCG administration was 22.4%. Over the three cycles, pregnancy was achieved in 39.5% of patients.[12]

What is its tolerability profile?

Lutropin alfa was generally well tolerated in hypogonadotropic hypogonadal women undergoing fertility treatment,[9,12] with no relationship seen between the lutropin alfa dosage and the adverse event rate.[9] The majority of adverse events were of mild to moderate severity;[9,12] no serious adverse events were reported.[9]

Adverse events were reported in 42.4% of women receiving lutropin alfa 75 IU/day plus follitropin alfa (dosage not reported) and in 46.5% of patients receiving follitropin alfa alone in a pooled analysis of six clinical trials.[6] The most commonly reported treatment-emergent adverse events in lutropin alfa recipients included headache, nausea, ovarian hyperstimulation, breast pain, abdominal pain and ovarian cyst (figure 2).

Over 90% of injections were associated with no local reactions[8,12] or local reactions of only mild severity;[8] no symptoms suggestive of immune reaction were reported.[8] Lutropin alfa administration was not associated with significant changes in laboratory parameters.[8,12]

What is its current positioning?

Subcutaneous lutropin alfa, the first and currently only available formulation of human recombinant LH, is a valuable option in the treatment of infertility in certain women. Synthesis of lutropin alfa using recombinant DNA technology ensures a product that is free of urinary impurities and that provides consistent hormone content and between-batch quality.[1] In conjunction with follitropin alfa, lutropin alfa has been approved in numerous countries worldwide for the stimulation of follicular development in infertile women with profound LH deficiency (<1.2 IU/L)[6] or severe LH and FSH deficiency[4] (table I). Lutropin alfa promotes optimal follicular development in hypogonadotropic hypogonadal women and is generally well tolerated.

Although not yet approved in these indications, lutropin alfa with follitropin alfa may also be of benefit in promoting optimal follicular development in certain subgroups of normogonadotropic women, including those with an inadequate response to prior follitropin alfa monotherapy,[13,14] those who are older (age ≥35 years),[15,16] and those with profound LH downregulation or who require excessive exogenous

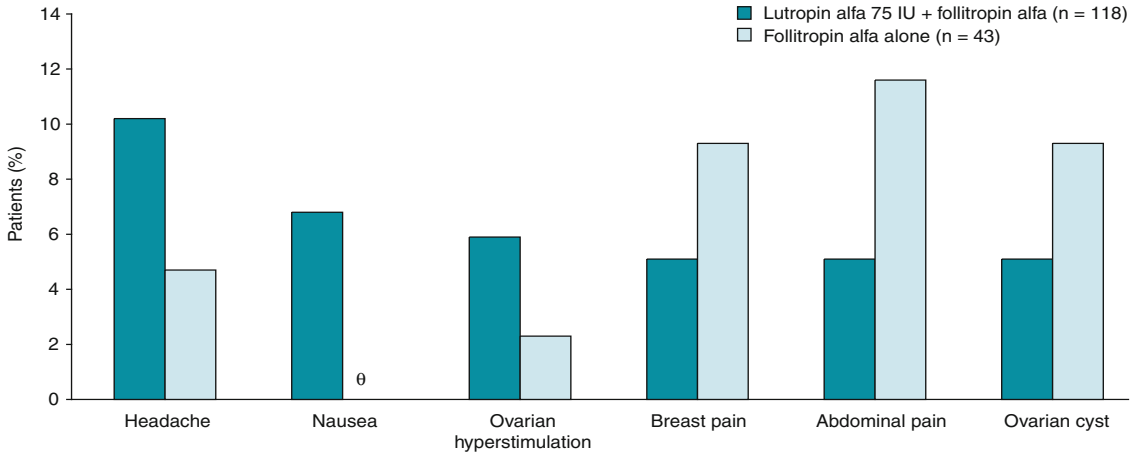

Fig. 2. Tolerability profile of lutropin alfa. Incidence (occurring in ≥5% of lutropin alfa recipients) of treatment-emergent adverse events in infertile hypogonadotropic hypogonadal women receiving subcutaneous lutropin alfa 75 IU/day plus follitropin alfa (dosage not reported) or follitropin alfa alone in a pooled analysis of six clinical studies.[6] θ indicates zero.

follitropin alfa.[17] However, one study in older women did not show any advantage of lutropin alfa supplementation.[18]

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