Pharmacology, pharmacokinetics and pharmacodynamics of different FSH preparations

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Fifth World Congress on Ovulation Induction, Rome, September 13 to 15, 2007
Different classes of FSH preparations

A. Human-derived and recombinant HMW preparations (market)
B. Long-acting, recombinant, HMW preparations (clinical development)
C. Oral, LMW preparations (preclinical development)

Molecular structure
FSH receptor interaction
In vitro and in vivo preclinical pharmacology
Human pharmacokinetics
Human pharmacodynamics
Molecular structure of FSH

α-subunit is common
β-subunit is specific

4 N-linked carbohydrate side chains

92 amino acids

111 amino acids
Human FSH receptor complex

Extracellular domain
349 aa

264 aa

65 aa
Intracellular domain

Fan et al, Nature 2005

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Carbohydrate site chains FSH

Protein → 0-1 Fucose → 1-4 GlcNAc → 1-4 Galactose → 1-4 Sialic Acid

Asn → Common: 3 Mannose

Common: 2 N-acetylglucosamine (GlcNAc)

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What is microheterogeneity?
Isoelectrofocusing of FSH preparations

- rFSH preparations have similar charge heterogeneity. *Horsman et al, 2000*

- compared to urinary FSH, rFSH contains a lower percentage of relative acidic isoforms. *Lambert et al, 1995*

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In vitro and vivo biological properties of FSH isoforms

- Acidic isoforms show a lower receptor affinity and lower intrinsic bioactivity than less acidic isoforms (Ulloa-Aguirre et al. 1988)

- Due to more branched oligosaccharides and a higher degree of sialic acid, acidic isoforms have a lower clearance rate (Blum and Gupta, 1985; De Leeuw et al 1996).

- Differences in sialic acid affect the in vivo bioactivity (rat Steelman Pohley assay).
FSH isohormones have different in-vivo bioactivity

Mulders et al, 1997

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Pharmacokinetic behaviour in the Beagle dog

rFSH isohormone fractions

Modified from De Leeuw et al, 1996

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Induced multiple follicle growth by daily FSH
Human pharmacokinetics of rFSH

7-day multiple dose study in pituitary-suppressed volunteers

- $T_1/2 = 28 - 34$ hrs
- $T_{max} = 10 - 12$ hr
- $F = 78\%$

Mannaerts et al, 1996

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Factors influencing exposure to exogenous FSH

- Gender
- Endocrine status
- Body weight
- Route of administration
- Injection device
- FSH dose
- FSH isohormone profile
- FSH immunoassay

Mannaerts et al 1993; 1996
Human pharmacodynamics of FSH
7-day multiple dose study in pituitary-suppressed volunteers

rFSH 150 IU

uFSH 150 IU

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Mannaerts et al., 199
Long-acting corifollitropin alfa

Corifollitropin alfa is a novel recombinant gonadotrophin molecule in development, in which the FSH-β chain is fused with the carboxy-terminal peptide of the hCG-β subunit.

Corifollitropin alfa is a new class of drugs with the proposed drug class name Sustained Follicle Stimulants (SFS).
Molecular structure of corifollitropin alfa

Amino acid (AA) sequence:
- No deviation from human sequence
- No additional linkage AA

Carbohydrate side chains:
- 4 N-linked similar to FSH
- 4 O-linked similar to hCG
In vitro and in vivo preclinical pharmacology
corifollitropin alfa vs Puregon®

- No intrinsic LH/hCG activity
- Approximately 1.5 times lower receptor binding activity and therefore in vitro bioactivity
- Two times higher in vivo bioactivity
- Four times higher ovulatory potential in immature rats
- Pharmacokinetics in dogs:
  - lower clearance rate
  - prolonged half-life (T$_{1/2}$: 43 hrs vs Puregon® 29 hrs)
Pharmacokinetic behaviour in the Beagle dog

- Puregon/Follistim i.m.
- Org 36286 i.v.
- Org 36286 i.m.

FSH immuno-activity (Delfia IU/l)

Hours after injection

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# Pharmacokinetics of corifollitropin alfa

women of reproductive age

<table>
<thead>
<tr>
<th></th>
<th>Corifollitropin alfa</th>
<th>Puregon®</th>
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</thead>
<tbody>
<tr>
<td>Elimination half-life</td>
<td>60-75 hrs</td>
<td>28-34 hrs</td>
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<tr>
<td>$T_{\text{max}}$</td>
<td>36-48 hrs</td>
<td>10-12 hrs</td>
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<tr>
<td>Apparent volume of distribution</td>
<td>~22 L</td>
<td>~30 L</td>
</tr>
<tr>
<td>$F$</td>
<td>-</td>
<td>78%</td>
</tr>
</tbody>
</table>

The single dose pharmacokinetics of corifollitropin alfa are dose-proportional within the dose-range tested (60 to 240 µg).
Corifollitropin alfa one-week regimen

FSH Activity

Stimulation days

1 2 3 4 5 6 7 8 9

threshold

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Mean # follicles on treatment day 8

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Dose-finding trial of corifollitropin alfa

Estradiol

Inhibin-B

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Effect of body weight on inhibin-B

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Dose selection of corifollitropin alfa for a one-week interval

Modeling and Simulation, including:
  * Pharmacokinetics, exposure first week and thereafter
  * Initial follicular response, reflects response to Org 36286
  * Number of oocytes, reflects response to regimen
  * Inhibin-B levels, sensitive marker for (lack of) stimulation
  * Covariate analysis, e.g. age, body weight, dose, GnRH analogue

Corifollitropin alfa is developed in two therapeutic strengths:
  * 100 µg for patients with body weight ≤ 60 kg
  * 150 µg for patients with body weight > 60 kg

*De Greef et al, ESHRE 2007, Abstract O-099*
LMW FSH agonists

Follicle-Stimulating Hormone

Disulfide bridges

Glycosylation at Asn-57 and Asn-78 of the α-subunit

Glycosylation at Asn-7 and Asn-24 of the β-subunit

LMW agonist
Receptor interaction by LMW FSH molecules
LMW FSH agonists

- Compound homogeneity; more consistent pharmacological response?
- Different receptor interaction; new insight into pharmacology and genetics?
- Tailor-made elimination half-life; improved efficacy and safety?
- Oral administration; for ease of administration!

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