Recombinants versus Biosimilars in Ovarian Stimulation

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Abstract

Biosimilars, also known as follow-on biologics, are biologic medical products whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods. Recombinant human follicle-stimulating hormone (r-hFSH) was one of the early biologic drugs to be approved and is used in assisted reproductive technologies (ART), sometimes known as in vitro fertilization. The drug was first marketed as Gonal-F by Merck Serono but has lost its European patent some time ago, US patent extends to 2015. In 2014, two FSH biosimilars obtained marketing authorization by the European Medicines Agency. Biosimilar FSH preparations are expected to be biologically and clinically "non inferior" to the originator product. However, prescribing a biosimilar to a patient calls for certain basic understanding by physicians of the scientific factors associated with the safety and efficacy of these products. Substituting an innovator brand by a biosimilar brand calls for caution in terms of quality, safety, and efficacy aspects due to clear differences between biosimilars and their reference products. The impact of FSH and human chorionic gonadotropn (hCG) biosimilars on cost and outcomes of ART is far from being established, since insufficient information is available to demonstrate the pros and cons in the long-term application.

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Introduction

Limited access to high-quality biologics due to the cost of treatment constitutes an unmet medical problem globally. The term "biosimilar" is used to designate a follow-on biologic that meets the extremely high standards for comparability or similarity to the originator biologic drug that is approved for use for the same indications [1]. Biosimilars (or follow-on biologics) are terms used to describe officially approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product [2]. Biosimilars are also referred to as subsequent entry biologics (SEBs) in Canada [3]. Reference to the innovator product is an integral component of the approval.

Use of biosimilar products has already decreased the cost of treatment in many regions of the world, and now a regulatory pathway for approval of these products has been established in the USA. The Food and Drug Administration (FDA) led the world with the regulatory concept of comparability, and the European Medicines Agency (EMA) was the first to apply this to biosimilars. Patents on the more complex biologics, especially monoclonal antibodies, are now beginning to expire and biosimilar versions of these important medicines are in development. The new Biologics Price Competition and Innovation Act allows the FDA to approve biosimilars, but it also allows the FDA to lead on the formal designation of interchangeability of biosimilars with their reference products [4]. The FDA's approval of biosimilars is critical to facilitating patient access to high-quality biologic medicines, and will allow society to afford the truly innovative molecules currently in the global biopharmaceutical industry's pipeline [4].

Unlike the more common small-molecule drugs, biologics generally exhibit high molecular complexity, and may be quite sensitive to changes in manufacturing processes. Follow-on manufacturers do not have access to the originator's molecular clone and original cell bank, nor to the exact fermentation and purification process, nor to the active drug substance. They do have access to the commercialized innovator product. Differences in impurities and/or breakdown products can have serious health implications [1]. This has created a concern that copies of biologics might perform differently than the original branded version of the product. Consequently, only a few subsequent versions of biologics have been authorized in the USA through the simplified procedures allowed for small-molecule generics, namely, Menotropins (January 1997) and Enoxaparin (July 2010), and a further eight biologics through the 505(b) [2] pathway [5].

Biosimilars can only be authorized for use once the period of data exclusivity on the original "reference" biological medicine has expired [1, 5]. In general, this means that the biological reference medicine must have been authorized for at least 10 years before a similar biological medicine can be made available by another company. For biosimilar medicines, the company needs to carry out studies to show that the medicine is similar to the reference medicine and does not have any meaningful differences from the reference medicine in terms of quality, safety, or efficacy. As information on the reference medicine is already available, the amount of information on safety and efficacy, needed to recommend a biosimilar for authorization, is usually less than the amount needed to authorize an original biological medicine. As with all medicines, the European Medicines Agency continues to monitor the safety of biosimilar medicines once they are on the market [1, 5].

None of the biosimilars were reported to have evidence of significant clinical variation relative to reference compounds in the absence of corresponding differences in biophysical properties

[5]. A recent study provides evidence that current EU guidelines have resulted in the approval of biosimilar therapeutics with comparable efficacy and safety profiles for the recommended indications of their respective reference originator biologics. It is anticipated that these precedents will serve as a starting point in the development of a process for approving biosimilars worldwide to provide efficacious and tolerable biotherapeutics with a significant cost advantage for national health care programs and consumers [5].

Discussion

Follicle-stimulating hormone (FSH) is a glycoprotein hormone essential for reproduction, both in females and males, and it is physiologically produced by the anterior pituitary gland in several isoforms. This heterogeneity is also typical of FSH-containing compounds, both urinary-derived and recombinant products. These compounds are widely used in assisted reproductive technologies (ART), to induce multifollicular development. Recently, the increased cost pressure on healthcare systems and the patent expiration date of widely used biotechnology-derived, recombinant FSH prompted the pharmaceutical interest in FSH biosimilars.

Recombinant human FSH (rh-FSH) is an important drug in Reproductive Medicine. Thorough analysis of the heterodimeric heavily glycosylated protein is a prerequisite for the evaluation of production batches as well as for the determination of "essential similarity" of new biosimilars [6]. The concerted application of different liquid chromatography-mass spectrometry methods enabled the complete depiction of the primary structure of this pituitary hormone. Sequence coverage of 100 % for the α- as well as the β-chain was achieved with tryptic peptides. Most of these peptides could be verified by tandem mass spectrometry. Quantification of the glycoforms of each glycopeptide was accomplished with the software MassMap®. The currently marketed product Gonal-F™ and a potential biosimilar were compared with the help of these procedures [6].

Ruman et al. [7] evaluated the efficacy of two novel long-acting rhFSH analogs, rh-FSH-N2 and rhFSH-N4, in stimulating murine folliculogenesis. Recombinant hFSH-N2 and -N4 were administered via single IP injection to 3-week-old female mice ($n=10$) that were killed 48 h later for dissection and histologic examination of reproductive organs and serum inhibin A. Results were compared with other groups of mice that received either single or q 12 h injections for 48 h of commercial rhFSH, or a single injection of pregnant mare serum gonadotropin (PMSG). A subgroup of the mice receiving rh-FSH-N4 was supplemented with daily injections of small doses of hCG to simulate LH add-back. Recombinant human FSH-N2 and -N4 administration induced a statistically significant increase in ovarian weights, uterine weights, and inhibin A levels compared with single and twice-daily injection of rhFSH. PMSG induced the greatest increases in all three measured parameters. There was no statistical difference between rhFSH-N2 and rhFSH-N4 for any parameter analyzed. A single injection of rhFSH-N2 or -N4 induced a greater number of antral follicles than did either single or q 12 h injections of rhFSH. The addition of small doses of hCG to rhFSH-N4 increased inhibin A levels and antral follicle number to reach statistical equivalence to PMSG treatment. The authors concluded that addition of a synthetic polypeptide containing two or four N-linked glycosylation sites to rhFSH increases in vivo bioactivity of the hormone compared to commercial rhFSH. After a single injection, both rhFSH-N2 and rhFSH-N4 effectively induced a greater follicular response in the mouse than did rhFSH [7].

Kim et al. [8] formulated a study to develop efficient Chinese hamster ovary (CHO) cells that express rhFSH in serum-free conditions and to investigate the effect of this newly synthesized rhFSH on folliculogenesis and ovulation. A stable single CHO cell that expresses rhFSH at a high level was obtained by introducing the human chorionic gonadotropin (hCG) alpha-subunit and FSH beta-subunit genes. After purification processing, they investigated the effect of this newly synthesized rhFSH on folliculogenesis in

hypophysectomized rats and ovulation in androgen-sterilized mice. The ovary weight, uterine weight, number of follicles, and ovarian morphology were evaluated in immature hypophysectomized rats. The number of ovulated oocytes and ovarian morphology were examined in androgen-sterilized mice. After purification processing, they analyzed the new rhFSH using matrix-associated laser desorption ionization-time of flight and found that this new rhFSH increased both ovarian weight and uterine weight in hypophysectomized rats and induced ovulation in androgen-sterilized mice. The study concluded that the newly synthesized rhFSH can be safely used in anovulatory infertile woman as well as in ovulation induction protocols for subfertile women [8].

Moon et al. [9] compared the efficacy and safety of a new rhFSH (FSH; DA-3801) with Follitropin-alpha (Gonal-F) in women undergoing controlled ovarian hyperstimulation (COH) for ART. This was a phase III, multicenter, randomized, non-inferiority study. A total of 97 women were randomized to receive COH using DA-3801 (DA-3801 group, $n=49$) or Gonal-F (Gonal-F group, $n=48$). All subjects underwent COH using a gonadotropin-releasing hormone (GnRH) antagonist protocol. The primary efficacy endpoint was the number of oocytes retrieved, and the secondary efficacy endpoints included the total dose of FSH, the duration of stimulation, the serum estradiol levels on the day of hCG administration, and the fertilization, implantation, and pregnancy rates. Safety was evaluated using pre- and post-treatment laboratory tests and all adverse events were recorded. The number of oocytes retrieved was 13.0 ± 6.2 (DA-3801) versus 10.6 ± 6.7 (Gonal-F) in the intention-to-treat (ITT) population, and 12.7 ± 6.4 (DA-3801) versus 11.0 ± 7.1 (Gonal-F) in the per-protocol (PP) population. The non-inferiority of DA-3801 was demonstrated with differences of 2.3 ± 6.5 (95 % confidence interval [*CI*] = 0.13, infinity) and 1.7 ± 6.7 (95 % *CI* = −0.74, infinity), respectively, in the ITT and PP populations. The total dose of FSH used (1789.8 ± 465.5 vs 2055.6 ± 646.7 pg/mL, $P=0.027$) and duration of stimulation (8.3 ± 1.4 vs 9.1 ± 1.9 days, $P=0.036$) in the ITT population were significantly lower in the DA-3801 group. Other secondary efficacy endpoints, including pregnancy and implantation rates and the incidence and severity of adverse events, were comparable between the two groups. The results of this study demonstrate that DA-3801 is not inferior to Follitropin-alpha in terms of its efficacy and safety in women undergoing COH for ART [9].

Choi [10] presented the first clinical results of biosimilar rhFSH in 2006 on the efficacy and safety of LG rhFSH (LBF0101) versus Follitropin-alpha (Gonal-F) in IVF/ICSI cycles. The number of oocytes retrieved by LG rhFSH was not significantly different to that by Gonal-F (12.3 ± 5.9 vs $4.2 =/- 8.6$). LG rhFSH was equivalent to Gonal-F in terms of secondary efficacy parameters. LG rhFSH and Gonal-F did not show significant difference regarding adverse events and local reactions to injection [10].

A new recombinant Follitropin was developed as a mixture of heterodimeric alpha and beta subunits by LG Life Sciences (Seoul, Korea). Koong et al. [11] conducted a study to evaluate the efficacy of the new recombinant Follitropin (LBFS0101) in an in vitro fertilization-embryo transfer (IVF-ET) program. Between April and July 2005, 28 cycles of COH-IVF were included in this prospective study. The patients were randomly divided into LBFS0101 ($n=15$) and Gonal-F ($n=13$) groups. COH was performed with GnRH agonist, and ovarian response was monitored by transvaginal sonography (TVS) and estradiol (E2) concentrations. Outcomes of fertilization and pregnancy were compared. Production of anti-FSH antibodies by injected recombinant FSH was monitored in the patient's serum before and after COH-IVF using ELISA. There was no statistical difference between two groups in the ovarian response, such as duration of stimulation, number of follicles, and serum E2 concentration on the day of hCG injection. There was no statistical difference in pregnancy and fertilization rates [11].

Lee et al. [12] analyzed the efficacy and tolerability of Follitropin-heterodimeric alpha-beta subunit mixture (LBFS0101; LG Life Sciences Ltd Seoul, Korea), new rhFSH preparations,

for superovulation in patients undergoing IVF-ET. One hundred and three infertile women undergoing IVF-ET in 2005 were enrolled into the study. After downregulation with Buserelin acetate, patients were randomized to receive LBF0101 ($n=52$) or Gonal-F ($n=51$). rhFSH was administered at 150–300 IU/day for 3–5 days, and then dosages were adjusted according to the ovarian response. A total of 15 cycles were cancelled, and 88 cycles (LBFS0101 = 47 cycles; Gonal-F = 41 cycles) were studied. There were no statistically significant differences in any clinical profiles of patients between the two preparations. Also, cumulative dose of rhFSH (2371.3 =/− 728.4 mIU for LBFS0101 vs 2409.8 ± 769.4 mIU for Gonal-F), duration of rhFSH treatment (9.3 =/− 4.6 days vs 10.6 =/− 5.8), and number of retrieved oocytes (14.2 =/− 9.1 vs 14.4 =/− 8.8) were not different. Clinical pregnancy rates and implantation rates were similar [44.7 % (21/47), 22.1 % (38/1690 for LBFS0101 and 56 % (23/41), 29.55 (941/139) for Gonal-F]. Anti-FSH antibody was not detected in all samples. The authors concluded that the results of their clinical study indicate that LBFS0101 may be suitable for use in ovarian stimulation for human IVF-ET programs [12].

FINOX Biotech (Finox AG) announced in 2012 that the pivotal phase III study (FIN3001) with Afolia, a biosimilar recombinant follicle-stimulating hormone (r-FSH), in patients undergoing ART, has met its primary endpoint [13]. Afolia is a new "biosimilar" medicine, an almost exact copy of the originator product that was produced using recombinant DNA technology. Both Afolia and the reference product Gonal-F are formulations of the naturally occurring hormone FSH, which plays a key role in human reproduction. Afolia is the result of a targeted drug development process, aimed to replicate as closely as possible the reference product. Afolia demonstrated clinical and statistical equivalence to the reference product Gonal-F. Equivalence was defined by retrieving similar numbers of oocytes during standard treatment duration of 10–16 days with a fixed dose of r-FSH. The equivalence margins required that the difference in the number of oocytes retrieved not exceed ±2.9 oocytes. Results prove that Afolia is "biosimilar" to Gonal-F: the number of oocytes retrieved was 11.3 in the AFOLIA group, compared to 10.8 in the Gonal-F group. The treatment difference was 0.52 with a 95 % CI of −0.81 to 1.79. The predefined equivalence margin was met. FIN3001 was an assessor-blinded, multicenter, phase III study, including a total of 410 patients in a 2:1 randomization scheme in favor of Afolia. The treatment effect and the safety profile of Afolia in controlled ovarian stimulation were compared to the widely used reference medicine, Gonal-F. Secondary endpoints included the number of days treated with FSH, the total dose of FSH received, the quality of oocytes retrieved, the quality of embryos transferred, and other important clinical parameters for ART. The results from the secondary endpoints were also similar in both treatment groups [13].

Recombinant hCG (r-hCG) had been initially manufactured by transfecting non-human cell lines (Chinese hamster ovary cells) with genetic material capable of replicating identical amino acid sequences to the human compound and developed as a pharmaceutical product named Ovidrel® (Merck Serono, Switzerland). Today, you have biosimilar molecules available in India (Triggerix®, Lupin Pharma, India).

Human chorionic gonadotropin is a therapeutic protein used for ovulation induction in women with infertility. Dong-A Pharm. Co. has developed r-hCG [product code DA-3803], produced in Chinese hamster ovary cells, and evaluated its biologic properties, such as biologic potency, efficacy, and pharmacokinetic profile, compared with a reference product, Ovidrel® [14]. The purpose of a recent study was to evaluate the efficiency of the purification process of Dong-A rhCG (DA-3803) and its bioequivalence from a biosimilar perspective. To confirm bioequivalence, the in vivo/in vitro biologic potency, ovulation induction rate, and pharmacokinetic profile of DA-3803 were compared with those of Ovidrel®. DA-3803 showed equivalent potency with Ovidrel®, and similarity between DA-3803 and Ovidrel® was observed in an efficacy evaluation that measured ovulation induction [14].

Conclusion

A similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use. Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules, such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. Owing to affordability and easy accessibility, biosimilars have established a good reputation among healthcare professionals. Though biosimilars are gaining popularity in national and international markets, it is important to remember that the biosimilars are not biological generics. These are rather unique molecules which are supported by only limited clinical data at the time of approval [15]. Therefore, there are concerns regarding their efficacy, long-term safety, and immunogenicity. At present, India is one of the leading contributors in the world biosimilar market. India has demonstrated the greatest acceptance of biosimilars, which is reflected from over 50 biopharmaceutical brands getting marketing approval [16]. The Indian biotechnology industry is also gaining momentum, with revenues of over US $2.0 billion reported in 2006, 70 % of which were biopharmaceuticals [17, 18]. According to a report, published in May 2014, by Visiongain, a business information publisher and consultancy in London, the world market drug revenues for biosimilars and related follow-on biologics will reach $9.2bn in 2018, and multiply in size to 2024, the fastest growth expected to be experienced within the submarkets for biosimilar monoclonal antibodies (mAbs) and insulins [19].

References

1. Hincal F. An introduction to safety issues in biosimilars. Follow-on biopharmaceuticals. J Med CBR Def. 2009;7:1–17.
2. Nick C. The US biosimilars act: challenges facing regulatory approval. Pharm Med. 2012;26(3):145–52. doi:10.1007/bf03262388.
3. Blanchard A, D'Iorio H, Ford R. "What you need to know to succeed: key trends in Canada's biotech industry" BIOTECanada Insights, Vol. 1 2010.
4. McCamish M, Woollett G. Worldwide experience with biosimilar development. MAbs. 2011;3(2):209–17. Epub 2011 Mar 1.
5. Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. Clin Ther. 2012;34(2):400–19. doi:10.1016/j.clinthera.2011.12.005. Epub 2012 Jan 13.
6. Grass J, Pabst M, Chang M, Wozny M, Altmann F. Analysis of recombinant human follicle-stimulating hormone (FSH) by mass spectrometric approaches. Anal Bioanal Chem. 2011;400(8):2427–38.
7. Ruman JI, Pollak S, Trousdale RK, Klein J, Lustbader JW. Effects of long-acting recombinant human follicle-stimulating hormone analogs containing N-linked glycosylation on murine folliculogenesis. Fertil Steril. 2005;83 Suppl 1:1303–9.
8. Kim DJ, Seok SH, Baek MW, Lee HY, Juhn JH, Lee S, Yun M, Park JH. Highly expressed recombinant human follicle-stimulating hormone from Chinese hamster ovary cells grown in serum-free medium and its effect on induction of folliculogenesis and ovulation. Fertil Steril. 2010;93(8):2652–60. doi:10.1016/j.fertnstert.2009.05.009. Epub 2009 Jun 16.
9. Moon SY, Choi YS, Ku SY, Kim SH, Choi YM, Kang IS, Kim CH. Comparison of the efficacy and safety of a new recombinant human follicle-stimulating hormone (DA-3801) with follitropin-alpha (Gonal-F) in women undergoing controlled ovarian hyperstimulation for assisted reproductive technology. J Obstet Gynaecol Res. 2007;33(3):305–15.
10. Choi DH. Efficacy & safety of LG Recombinant Human FSH (LBF0101) versus Follitropin Alpha (Gonal-F) in IVF/ICSI cycles. A multi-center, open, randomized comparative clinical trial. Abstract Book: The 5th Binannual meeting of Pacific Rim Society for Fertility & Sterility. 2006, p. 56.
11. Koong MK, Kim HO, Choi SJ, Lee SH, Kang HJ, Yang KM, Song IO, Kang IS, Jun JH. Efficacy of new recombinant follitropin (LBFS0101) in a controlled ovarian hyperstimulation and in vitro fertilization program. Hum Reprod Abstracts of the 22nd Annual Meeting of the ESHRE, Prague, 2006, p. 331, pp. 543.
12. Lee W, Koong M, Kim H, Choi D, Park L, Yoon T. Effect of LBFS0101, a new recombinant FSH in human IVF-ET program: a prospective and randomized clinical study. Hum Reprod Abstracts of the 22nd Annual Meeting of the ESHRE, Prague, 2006. p. 518, pp. 809.
13. A Phase III Study to Compare Efficacy and Safety of AFOLIA vs. Gonal-f® in Infertile Women 35 to 42 Years of Age Undergoing in Vitro Fertilization (IVF) (FIN3002). ClinicalTrials.gov identifier: NCT01687712. http://clinicaltrials.gov/show/NCT01687712.

14. Seo KS, Yoon JW, Na KH, Bae EJ, Woo JG, Lee SH, Kang SH, Yang JM. Evaluation of process efficiency and bioequivalence of biosimilar recombinant human chorionic gonadotropin (rhCG). BioDrugs. 2011;25(2): 115–27. doi:10.2165/11589430-000000000-00000.
15. Nowicki M. Basic facts about Biosimilars. Kidney Blood Press Res. 2007;30:267–72.
16. Mody R, Goradia V, Gupta D. How similar are Biosimilars in India? A blind comparative study. Available from: http://www.pharmafocusasia.com/research_development/blind-comparative-study.html. Last accessed on 1 June 2010.
17. Thomas TK. Patent for biosimilar drugs may be made mandatory. The Hindu Business Line (Published on May 06, 2008). Available from: http://www.thehindubusinessline.in/2008/05/06/stories/2008050651531000.htm. Last accessed on 1 June 2010.
18. OPPI position paper on 'Biosimilar' in India. Available from: http://www.indiaoppi.com/oppibiosimilars.pdf. Last accessed on 1 June 2010.
19. Biosimilars and Follow-On Biologics: World Industry and Market Prospects 2014-2024, https://www.visiongain.com/Report/1253/Biosimilars-and-Follow-On-Biologics-World-Industry-and-Market-Prospects-2014-2024.