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Feature

Overlapping biosimilar and originator follitropin alfa preparations: How much closer can they get?

Fernando de Mora [a,*], Colin M. Howles [b]

Unfounded skepticism relating to biosimilars, arising from the assertion that they are not molecularly identical to their original counterpart, fails to acknowledge that no biological medicine, including Gonal-f® (from Merck Serono) is identical to itself. Molecular differences between the biosimilar and the reference medicines are irrelevant and clinically undetectable as long as they are contained within the accepted variability for the original medicine. Accordingly, the minor differences in 'ongoing pregnancy rate' and 'live birth' rate reported in a recent meta-analysis of biosimilars of Gonal-f® from Chua et al. are probably driven by product-unrelated factors, notwithstanding the fact that of the four products under analysis, only Ovaleap® (from Theramex UK Ltd) and Bemfola® (from Gedeon Richter Plc) can unambiguously be considered to be biosimilars. The EU Biosimilars model has proven successful, but some healthcare professionals, building on highly arguable premises, voice a distrust in biosimilars. Only if such scientifically unfounded distrust is reverted, the full promise of rFSH alfa biosimilars for reproductive medicine patients is likely to be fulfilled.

Keywords: Bemfola®; Biosimilar; Follitropin alfa; Gonal-f®; Ovaleap®; Recombinant follicle-stimulating hormone; Reproductive medicine; rFSH; Follitropin beta

Biosimilars are biological medicines that have been shown to be essentially the same as an original reference product, according to stringent regulatory standards. Such products have brought demonstrable value to patients.[1] Notably, Ovaleap® (from Theramex UK Ltd) and Bemfola® (from Gedeon Richter Plc) are two biosimilars of the recombinant follicle-stimulating hormone (rFSH) or follitropin alfa product Gonal-f® (from Merck Serono). These two biosimilars were authorized in the European Union (EU) in 2013 and 2014, respectively, and elsewhere, and were rapidly shown to increase access to infertility treatment for women.[2] In parallel, early skepticism about rFSH biosimilars was exhibited by some healthcare professionals (HCPs). Despite efforts by the reference regulatory authorities and academics to reassure HCP on the science of biosimilarity, and on the interchangeable nature of a biosimilar and its original counterpart,[3] doubts still remain regarding the therapeutic performance of follitropin-alfa biosimilars, as revealed by a very recent paper.[4] By discussing and updating the scientific evidence, this feature article refutes the view that the authorized rFSH biosimilars exhibit clinically relevant differences with Gonal-f®; a view that, in the authors' opinion, is built on questionable premises.

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The science of rFSH biosimilar products: Learning from Gonal-f®

Skepticism about biosimilars of Gonal-f® from some HCP arose from the assertion that "*biosimilars are not exact copies*" of their original counterpart.[5] Such a statement is taken out of context, however, since even original biological medicines are not 'identical to themselves'. Indeed, in 2003, the developers of Gonal-f®[6] had already disclosed the inherent batch-to-batch structural heterogeneity of the original rFSH product. Expectedly, the Gonal-f® batch-to-batch variation in sialylation was not paralleled by variation in the clinical behavior, and did not trigger discomfort among HCP. The fundamental scientific principle that clinical 'sameness' between two versions of a given biological medicine may arise despite non-molecular identicality is well established. Notably, in a 2017 paper,[7] Merck, the current marketing authorization holder (MAH) for Gonal-f®, acknowledged that "*variability of product characteristics is intrinsic to complex living cell production processes, and acceptable changes in quality attributes have been described*". Accordingly, despite broader molecular differences between them, the first-to-market original rFSH preparations Gonal-f® (alfa) and Puregon® (beta) exhibit no evidence of significant clinical divergence.[8,9] All this shows that comparisons in a clinical setting are therefore much less sensitive than analytical comparisons for picking up minute differences between versions of a given biologic, given the fact that those minor differences are often irrelevant from a therapeutic perspective.

Because of the reliance on the certainty that function follows form, biosimilarity needs to be demonstrated through a comprehensive comparability analysis that ascertains the essential molecular overlap between the biosimilar candidate and the reference medicine (as we have extensively reviewed for rFSH products[10]) The acceptable level of difference between a biosimilar candidate and its reference medicine is determined by a thorough assessment of multiple batches of the reference biologic. Consequently, the most sensitive way to demonstrate that rFSH biosimilar preparations and Gonal-f® have equivalent efficacy and safety is to show that their differences in critical structural and functional attributes do not exceed the intrinsic structural variability of the original medicine. Indeed, extensive analytical comparisons can identify molecular fluctuations that would otherwise remain clinically undetected because of inter-patient variability in treatment response. Therefore, the common claim that the pre-authorization clinical comparability assessment needs to be extended lacks scientific foundation. The understanding that close analytical comparability predicts clinical comparability was obtained from studies of the unwanted intrinsic heterogeneity of original biologics. Indeed, comparability is a well-established scientific principle that has been used for decades to evaluate changes in manufacturing, or composition, that occur during the commercial life cycle of biotechnological medicines.[11].

In reality, the development of an original candidate product and the replication of an existing product, for which extensive knowledge has accumulated, logically should not follow the same experimental path. Randomized clinical trials (RCTs) are advocated as the gold standard for demonstrating the therapeutic benefit of new products, but they have very limited value in showing the comparability of highly similar biologic medicines. Accordingly, industry representatives from Merck, a company active in the reproductive medicine field declared[7]: "*Much greater analytical scrutiny and in-depth functional characterization are required for the approval of a biosimilar…as these are the foundations for comparable safety and efficacy performance in the clinic.*" The questionable value of RCTs in demonstrating biosimilarity has recently been stressed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA)[12]: "*…an efficacy trial in patients is not expected to show differences undetected by extensive analytical testing*" and "*…comparative efficacy trials are neither an effective discriminating tool for the comparison of the biosimilar with the reference product, nor an efficient use of limited resources*". Experts from the European Medicines Agency (EMA)[3] endorse the concept that RCTs are only confirmatory, rather than key to substantiating biosimilarity. Therefore, the optimal approach to uncovering biosimilarity is to demonstrate that differences in critical analytical attributes do not exceed the intrinsic heterogeneity of the original product, as reported for Ovaleap®.[13].

Biosimilar-to-originator rFSH: No evidence of clinical divergence

In light of the above, a recent meta-analysis conducted by Chua *et al.*,[4] which led the authors to conclude that biosimilar versions of Gonal-f® exhibit lower rates of 'ongoing pregnancy' and 'live birth' than the reference medicine, warrants further scrutiny. On the basis of the scientific principles summarized above, the clinical differences reported between biosimilars and Gonal-f® are very unlikely to be driven by the clinically acceptable minute molecular differences that were observed, as their analytical attributes essentially overlap. Instead, the clinical differences are more likely to be attributable to product-unrelated factors. Indeed, multiple factors, such as the hCG dose given to trigger final follicular maturation, the time interval between oocyte collection and fertilization subsequent to intracytoplasmic sperm injection (ICSI), the laboratory procedures followed, and even the individual embryo transfer operator,[14] among others, probably do impact the analyzed endpoints. Consequently, in the context of the confirmatory nature of a clinical comparability exercise, the 'ongoing pregnancy' or 'live birth' endpoints are of reduced value in confirming biosimilarity.

Ovarian stimulation is the well-characterized mechanism of action of rFSH, which gives rise to the drug's clinical effect. Thus, the recommended primary marker of efficacy, the number of 'oocytes retrieved', is the most reliable product-to-product comparability endpoint because it minimizes the bias introduced by the secondary factors mentioned above. In fact, the interpretation of the meta-analysis results challenges the well-established functional connection between 'oocytes retrieved' and 'pregnancy rate' or 'live birth' rate.[15] One could infer that, although the number of oocytes remains statistically equivalent, their quality may differ owing to physicochemical or functional differences among the products, such as differences in biological activity or glycopattern. This seems very improbable in light of both the thorough analytical comparative assessment of the biosimilar candidates (including isoforms

TABLE 1

Key evidence from clinical studies required for authorization of rFSH alfa-bearing biosimilars, from real world therapeutic performance of biosimilars, and of the value of biosimilars to reproductive medicine patients.

Scope	Study	Observations and conclusions
Safety and efficacy (Real World Evidence (RWE))	Rettenbacher *et al.*[16]	Safety and efficacy of Bemfola® (biosimilar follitropin alfa) for up to two treatment cycles in infertile women using assisted reproductive technology. The Phase III open label study demonstrated that Bemfola® and Gonal-f® have similar clinical efficacy and safety profiles.
	Strowitzki *et al.*[19]	Safety and efficacy of Ovaleap® (biosimilar follitropin alfa) for up to three cycles in infertile women using assisted reproductive technology: a Phase III open-label follow-up main study.
	European Medicines Agency & European Commission[20]	Document made public by the European healthcare authorities essentially for prescribers, in which the biosimilar concept is thoroughly revised. The EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicine.
	Sydow *et al.*[21]	Study in 34 reproductive medicine centers in Germany, in which the effectiveness and safety of ovarian stimulation with Ovaleap® in a gonadotropin-releasing hormone (GnRH) antagonist protocol was extended for the first time to real-world practice in assisted reproductive technology (ART) clinics.
	Griesinger *et al.*[27]	Study in 24 reproductive medicine centers in Germany and Austria, in which the effectiveness and safety of ovarian stimulation with Bemfola® in a GnRH antagonist protocol was extended to real-world ART clinical practice.
	Ferrando *et al.*[28]	Study in 26 ART centers in Spain, in which the effectiveness and safety of ovarian stimulation with Bemfola® in four distinct patient populations were recorded. The four populations studied were poor responders, suboptimal responders, normal responders and oocyte donors.
	Šprem Goldštajn *et al.*[29]	Single center study evaluating the efficacy of Ovaleap® with reference to Gonal-f ® in a GnRH fixed antagonist or flexible antagonist protocol.
Essential sameness	Cruz *et al.*[22]	The use of any follitropin alfa version (whether original or biosimilar) does not impact the number of oocytes retrieved from women.
	Van den Haute *et al.*[23]	Clinical outcome is not influenced by the product given—Ovaleap® (follitropin alfa) or Puregon® (follitropin beta)—as had been shown in earlier studies comparing Gonal-f® and Puregon®.
	Kaplan *et al.*[24]	Phase III trial comparing Ovaleap® and Gonal-f® in ART in a prospective cohort, showing that ovarian hyperstimulation syndrome (OHSS) and OHSS severity, as well as pregnancy and live birth rates, are similar for Ovaleap® and Gonal-f®.
	Bosch *et al.*[25]	Bemfola® (biosimilar follitropin alfa) has clinical efficacy similar to those of established recombinant follitropins in ART (either alfa or beta).
	Strowitzki *et al.*[26]	Safety and efficacy of Ovaleap® (biosimilar follitropin alfa) compared to Gonal-f® in the first ART treatment cycle. This Phase III open label study demonstrated that Ovaleap® and Gonal-f® have similar clinical efficacy and safety profiles.
Value substantiation	QuintilesIMS[2]	Early impact of the launch of rFSH alfa biosimilars: (i) increased patient access to fertility treatment measured in number of treatment days; and (ii) reduced overall cost of fertility treatment.

and biological activity studies), which showed that the minute differences in critical attributes are contained within the batch-to-batch variability found for Gonal-f®, and the fact that markers of oocyte and embryo quality are examined during the development of biosimilars, as per EMA guidance. Accordingly, no differences in oocyte quality were uncovered by a head-to-head study comparing the effects of biosimilars and original products.[16]

Alternative interpretations of the meta-analysis[4] may also be provided. Could the unexpected results be linked to the methodology? In spite of the usefulness of a meta-analysis meant to provide power by pooling data from homogeneous trials, the authors themselves admit to the moderate quality of their study. It is worth underlining at least three relevant methodological issues.

First, of the four products included in the analysis, only Ovaleap® and Bemfola® can unambiguously be considered biosimilars on the basis of the regulatory frameworks used in the regions where the products have been approved. Many agencies are not compliant with the evidence-based principles followed by the World Health Organization (WHO)-designated stringent regulatory authorities.[17] This signifies that the authors have gathered data from Ovaleap® and Bemfola® and data from products whose development may not have followed the same scientific standards (potentially substandard biologic products). This would put the validity of the authors' conclusions into question, as homogeneity is a key principle in meta-analysis methodology. Indeed, as also stressed by the current Gonal-f® marketing authorization holder[7], notwithstanding the fact that less stringent requirements may constitute a risk for patients, one should refer to a product as a 'biosimilar' when there is certainty that it has been developed following the scientific criteria pioneered by the EMA. Reference regulators themselves have warned about the need for utmost

rigor in designating a medicine as a 'biosimilar'.[18]

Second, disregarding the probable differences in development standards (and possibly in the standard operating procedures (SOP) of the centers involved), the number of patients (n) attained by combining the studies may be statistically acceptable, but it still seems too low to allow an undisputable conclusion to be reached, which may partly explain the moderate quality of the study undertaken. On the other hand, only data from three of the four pre-authorization RCT (one of them with an overly low number of patients) have been pooled to conduct the calculations, which certainly does not comply with what a standard meta-analysis would require under the stated conditions.

Third, an additional hurdle in our opinion is that the authors draw their conclusions by assessing the endpoints 'rates of ongoing pregnancy' and 'live birth' rate, in spite of the fact that the RCT that are included in their analysis were not designed to detect differences in such endpoints. This is because, on the basis of the scientific principles described above, 'oocytes retrieved' is the endpoint of choice for regulatory authorities because it minimizes the interference of confounding factors in a clinical comparability exercise. Even though a meta-analysis is meant to overcome the limitation imposed by low numbers of participants in each individual study, qualitative limitations, including the lack of a double-blind approach to evaluate the targeted clinical outcome, do remain.

All in all, the interpretation of Chua *et al.*[4] that "*treatment with biosimilar preparations of follitropin alfa is likely to result in lower probability of life birth, clinical and ongoing pregnancy compared with the reference product*" is questionable and, at the very least, should be put on hold. Instead of re-visiting pre-marketing clinical data, in the light of the extensive experience with the biosimilar preparations, the outcomes observed in clinical practice could now provide more conclusive evidence. Indeed, real-world evidence (RWE) from thousands of patients treated with high-standard follitropin-bearing products has been published to support the clinical sameness of the biosimilars Bemfola® or Ovaleap® and the original products Gonal-f® or even a follitropin beta (Puregon®) (Table 1).[19–29]

Conclusions

The lack of an accurate understanding regarding the science of biosimilarity may foster distrust in biosimilars among HCPs, whereas knowledge of the well-established scientific principles that guide the development of biosimilars raises confidence. Further to pre-launch evidence, as stated by the European Commission in a 2019 guide[20]: "*. . .the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines*". The EU biosimilars model has thus proven successful and cost-effective. The most notable impact of such cost-effectiveness is the potential for healthcare budgetary redistribution, which, for instance, has increased early patient access to fertility biological therapies. Furthermore, the reallocated funds may be used to improve healthcare services, to acquire technologic upgrades or innovative medicines, or to initiate biological therapy at earlier stages of a given disease. Stakeholders must acknowledge, however, that the advantages of biosimilars are more than monetary and have been bolstered by empirical validation throughout Europe since their inception in 2006.[1] The creation of patient registries that allow more data to be amassed through greater access will help to gauge the long-term effects of biosimilars on disease progression. Legal provisions also exist to encourage innovation within the biosimilars themselves, leading manufacturers to aim for greater stability, less immunogenicity, or easier and more efficient modes of delivery, as has been the case for follitropin alfa-bearing biosimilars.[30] Physicians should be reassured that EMA-approved follitropin-alfa-bearing biosimilars, such as Bemfola® and Ovaleap®, are a high-quality alternative to Gonal-f®. The merits of original biologics are not disputed, but biosimilars contribute principally to the sustainability of healthcare systems, thus ensuring that present and future patients are properly served. But as long as there is a scientifically unjustified resistance to the use of biosimilars that is built upon a biased foundation, the promise of rFSH alfa biosimilars is unlikely to be fulfilled.

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Prof. Fernando de Mora is full professor of pharmacology at the Universidad Autonoma de Barcelona, where he obtained a PhD in immunopharmacology. He worked as a postdoctoral fellow at Harvard Medical School, and shortly after obtained an MBA from the University of Chicago. Fernando is principal investigator in government-funded research projects on both the identification of new targets in asthma and novel approaches to biosimilar characterization. He acts as an academic consultant and speaker in biosimilar science and in the sphere of regulation and marketing in the biopharmaceutical industry, working with healthcare administrations and with public and private organizations.

Colin M. Howles is the founder of ARIES Consulting, based in Geneva, Switzerland. ARIES Consulting has been active since 2013 and provides services to companies in the Fertility therapeutic area as well as working directly with in-vitro fertilisation (IVF) clinics across the world. He is also an Honorary Fellow in the Deanery of Biomedical Sciences, University of Edinburgh where he participates in the undergraduate teaching program and research supervision. Dr. Howles has worked for 44 years in the field of Reproductive, Endocrinnology and Medicine. He obtained a PhD from Nottingham University, UK and started working at the first human IVF clinic in the world, Bourn Hall Clinic, Cambridge UK in the early 1980's. He then spent 25 years in the biopharmaceutical industry and was involved in the development and worldwide clinical introduction of the first recombinant h-FSH (follitropin alfa), h-LH (lutropin alfa) and hCG (choriogonadotropin alfa). In total, he had experience of introducing into clinical use six recombinant gonadotrophin preparations.

Fernando de Mora [a,*], **Colin M. Howles** [b]

[a] Departamento de Farmacología, Terapéutica y Toxicología, Universidad Autónoma de Barcelona, 08193 Bellaterra, Barcelona, Spain
[b] ARIES Consulting, Ch du Barbolet 5b, 1213 Onex, Geneva, Switzerland

* *Corresponding author.*