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Commentary

Biosimilars to recombinant human FSH medicines: comparable efficacy and safety to the original biologic

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A B S T R A C T

Two recombinant follicle-stimulating hormone (rFSH)-bearing similar biological medicines (biosimilars) have been authorized by the European Commission. Biosimilar is a regulatory concept alluding to the evidence-based high-standard comparability studies needed to demonstrate its equivalence to a reference original biologic. Because biosimilar development represents a shift from the long-lasting existing paradigms, a thorough understanding of the science behind it will contribute to helping prescribers make informed treatment choices. Contrary to chemically-synthesized medicines, biologics are subject to an inherent molecular variability. From the experience with original biologics, regulatory authorities have accumulated a wealth of knowledge as to what minor batch-to-batch physicochemical variations may be therapeutically acceptable in a given product. Furthermore, in spite of analytically detectable differences, the two original rFSH-bearing medicines currently on the market share fundamentally the same therapeutic profile. Unlike those original medicines, a biosimilar of an rFSH product and the corresponding reference biologic share essentially the same active pharmaceutical ingredient. They are also administered via the same route, at the same dose, and for the same indications. This article revises the background evidence over which the biosimilarity principle has been built, and highlights the therapeutic potential for follitropin biosimilars in order to reassure physicians on their benefit.

Biosimilars set in context

Broadly, biologicals or biologic medicines are products whose active pharmaceutical ingredient (API) is produced by a biological source. Until the late 20th century most biologicals were either extracted from organs – such as insulin from swine pancreas – or from human biological fluids such as plasma. Likewise, FSH has been isolated from human pituitary glands and urine. Since 1982, the production of biologicals has increasingly relied upon biotechnology, i.e. essentially, the genetic engineering of cells. Recombinant therapeutic proteins are biotechnology-derived biologicals. For instance, monoclonal antibodies, cytokines like filgrastim or IFN-beta, and hormones such as epoetins, are manufactured by means of recombinant technology. Biotechnology has been instrumental in bringing novel medicines into the pharmaceutical armamentarium. Notably follitropin, i.e. recombinant human FSH (rHuFSH or rFSH), first described in 1989, has greatly contributed to the advancement of infertility treatment (Macklon et al., 2006), and more recently, a hybrid biotech molecule with sustained follicle-stimulating activity – where the carboxyterminal peptide of human chorionic gonadotrophin was added to the β chain of rFSH – has been introduced into the clinic (Fauser et al., 2009).

Regardless of the therapeutic improvement attributable to biotech medicines, their price precludes access to these products to a significant segment of the global population (Putrik et al., 2014). The patent expiration of original biotech products has opened up a new

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window of opportunity for patients. Indeed, biologicals that contain essentially the same API as an original biomedicine, and that share its quality, safety and efficacy, may be developed: the so-called similar biologic medicines, or biosimilars (de Mora, 2015). Biosimilars are highly comparable to original products, but could be made available at a reduced price because existing background evidence allows for a customized development programme. However, the pathway established to ultimately demonstrate a favourable benefit-to-risk balance for biosimilars still casts doubt among some healthcare professionals (Weise et al., 2012), and such debate may lead to a suboptimal utilization of these products. Two biosimilars containing rFSH have already been granted a marketing authorization in Europe (Rettenbacher et al., 2015; Strowitzki et al., 2016). Understanding the stringent scientific and medical evidence behind biosimilars approval may play a part in optimizing their use.

FSH: acceptable inherent variability

The biological source, combined with its complex and unstable protein nature, inherently links biologicals to a structural variability that exceeds that of traditional non-biological chemically-synthesized medicines (the so-called small molecules). Protein production – either natural or *in vitro* – gives rise invariably to a mixture of molecular forms. Recognition of the intrinsic heterogeneity of such biologicals proceeded from the experience with original medicines, well before biosimilars came into play.

From endogenous to recombinant FSH heterogeneity

Endogenous FSH is a gonadotrophic hormone produced by the anterior lobe of the pituitary gland. It is a heterodimeric glycoprotein defined by its primary amino acid sequence, which is physiologically expressed as a heterogenous molecular entity as a result of differential carbohydrate expression, i.e. of sialic acid content (Macklon et al., 2006). Human pituitary gonadotrophin preparations first obtained in 1958 were used to stimulate ovarian follicle development. However, shortages and severe safety issues associated with pituitary extracts prompted the need to find alternative sources of FSH. In the early 1960s, FSH (and luteinizing hormone, LH) isolated from the urine of postmenopausal women was used for ovarian stimulation in anovulatory infertile women. The intrinsic heterogeneity of FSH was reflected in the urinary product, termed human menopausal gonadotrophin. In 1993, a highly purified (HP) FSH version with less urinary protein contaminants was marketed in Europe.

Biotechnology was then applied to human FSH production, and in 1996 the first follitropin alfa was launched, followed by follitropin beta. The two original rFSH medicines currently on the market present detectable differences in their physicochemical properties, attributable to their different cellular origin and manufacturing conditions, but they essentially give rise to the same therapeutic outcome. In spite of even wider physicochemical differences between urinary and rFSH, both preparations share a similar blood concentration profile. Hence, equivalent protocols and treatment regimens are applied. Moreover, a systematic review of the clinical outcome resulting from using either formulation did not uncover any significant differences in the live birth rate (van Wely et al., 2011). Recombinant technology brought to clinics preparations free from urinary protein contaminants, production of limitless amounts, and an increased batch-to-batch consistency compared with the urine-derived product, allowing for a new mass-based method of quantification. Nonetheless, batch-to-batch physicochemical heterogeneity in any recombinant therapeutic protein cannot be fully removed. Therefore, tight quality monitoring needs to be applied during production in order to ensure that intrinsic variability does not exceed the pre-specified limits, and does not have therapeutic consequences.

Biotech medicines: acceptable batch-to-batch variability

From the monitoring of the physicochemical attributes of biotechnology-derived biologics, industry and regulators have gained much knowledge as to which minor molecular batch-to-batch variations of recombinant therapeutic proteins may be therapeutically acceptable. Such knowledge emerges mostly from the comparability studies performed after manufacturing process changes in original biologics production occur. Process modification of commercialized biologics is a recurrent practice throughout the life cycle of any given medicine (Vezér et al., 2016). Physicochemical differences resulting from those manufacturing modifications may be found among batches of innovator biotech medicines. Notably, fluctuations of the glycosylation pattern – a common source of variability (Schiestl et al., 2011) that does not necessarily translate into alterations of safety or efficacy.

Indeed, although infrequent, certain manufacturing modifications may ultimately impact on the product's pharmacological features. The identification in the late 1990s of immunogenicity against an original epoetin induced by a change in the formulation illustrates this phenomenon (Casadevall et al., 2002). Reference regulatory bodies such as the European Medicines Agency (EMA) have issued guidance for marketing authorization holders to ensure that quality, safety and efficacy between the prior (pre-manufacturing) and the new (post-manufacturing) version do not significantly differ. Physicochemical comparability studies are normally sufficient to prove high comparability, given that they are the most sensitive assays to pick up subtle molecular changes. Original follitropin alfa, for instance, has been subject to production changes of different focus and magnitude as reported by regulatory authorities. Physicians should be reassured that, if the pre- and post-manufacturing versions of any biological are deemed comparable, the potential minor differences in the physicochemical attributes are therapeutically acceptable, and should be considered irrelevant in the context of the usual clinical variability; for instance the ovarian response to exogenous FSH. The comparability exercise set by the EMA for the identification of molecular differences among batches of original biologics set the stage for the issuance of a regulatory guidance for biosimilars (Weise et al., 2014), whose objective is to ascertain that the differences in the manufacturing process applied do not have any significant impact on the product's safety and efficacy.

Biosimilars: evidence-based equivalence

In spite of the physicochemical variability among currently available original FSH-bearing medicines, they share in essence the same therapeutic features. Accordingly, those structural differences have not had any impact on the physician's decision to prescribe either originator product. A medicine meant to replicate an existing biologic, hence a biosimilar, allows for a substantial reduction of the magnitude of those product-to-product differences found among originators.

Biosimilars: in essence the same

A biosimilar is designed from scratch to match a reference original biological, i.e. to be as close to the reference product as the reference is to itself from batch to batch over its life cycle (de Mora, 2015). The biosimilar bears in essence the same active substance, comes in the same pharmaceutical form, and is administered via the same route at the same dose for the same, or fewer, indications than the original counterpart. In 2005, the EMA put forward stringent regulatory grounds for biosimilars development (EMA (European Medicines Agency), 2014), and became the pioneer and most experienced regulatory body worldwide in this arena. Australian (Therapeutic Goods Administration, 2015), Canadian (Health Canada, 2016), Japanese (Arato, 2016) and agencies in other countries, including the USA's FDA (FDA (US Food and Drug Administration), 2015), followed with analogous regulatory frameworks standing over the same EMA scientific principles. The World Health Organization (WHO) also issued in 2009 a biosimilars document fundamentally replicating the EMA requirements (WHO (World Health Organization), 2009).

Figure 1 summarizes the rationale behind the differential regulatory pathways of biosimilars, original biologics and generics. A pharmaceutical company wishing to develop a biosimilar starts out with a bulk of background knowledge that permits it to build a customized development plan relying on evidence from the reference product. Briefly, the biosimilar developing company knows the amino acid sequence of the original product, i.e. the structural backbone of the API, and replicates it exactly. It may know the mechanism of action and the expected biological activity, and it can acquire, and reverse-engineer, the reference medicine to analyse its conformational structure, its composition, and its batch-to-batch structural and functional variability. But above all, it has access to a huge amount of real-world clinical evidence on its safety and efficacy profile. Together with the non-publicly available information held by the regulatory authorities, this accumulated knowledge drives the design of customized studies meant to reliably demonstrate a high comparability between the biosimilar candidate and the reference medicine, i.e. an equivalent benefit-to-risk balance. Therefore, once authorized, the biosimilar is just an alternative high-quality biological with a distinctive trait: its proven high equivalence to an existing original medicine.

Quality attributes: the foundation of biosimilarity

Acknowledging biosimilarity is a result of a comparability exercise lasting from 6 to 12 years, which comprises head-to-head quality, and preclinical and clinical studies, the ultimate goal of which is to exclude any relevant difference between the biosimilar and the reference medicinal product. The standard generic's development approach is not applicable to biosimilar candidates given that, contrary to a biologic, a chemically-synthesized API may be virtually identically replicated (**Figure 1**). A biosimilar is thus not a generic.

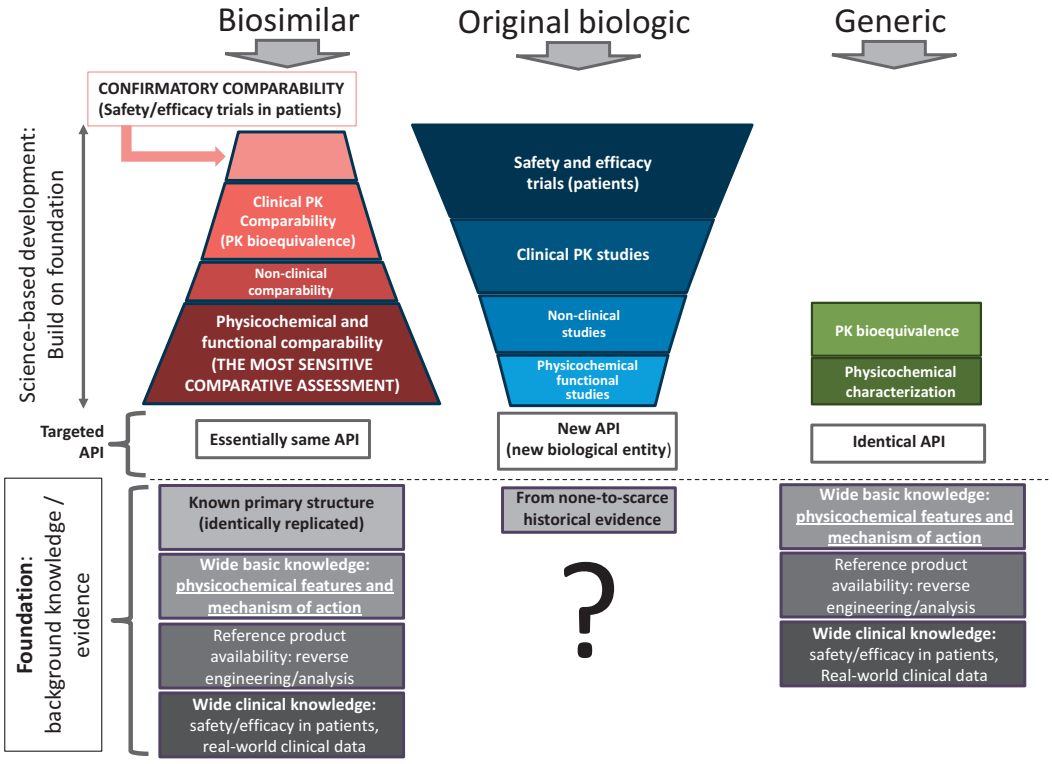

Figure 1 – The science behind the differential regulatory requirements for biosimilar, original biologic and generic medicines. The basis of the demonstration of equivalence between a biosimilar and the reference product relies on the physicochemical and biological activity comparability assessment (quality module). This is represented in the figure by means of a wider basal layer (dark red bottom layer). Conversely, the main demonstration of a favourable risk-to-benefit balance of an original biological resides in the late clinical trials in patients (dark blue top layer). Finally, given the fact that the active pharmaceutical ingredient (API) of a chemically-synthesized medicine can be virtually identically replicated, the generic development pathway may be considerably abridged (as represented by narrow green layers). In addition to the pre-authorization studies, an active pharmacovigilance program needs to be set for biosimilars approval as for any new biological or chemical entity. PK = pharmacokinetic. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In order to scrutinize potentially negligible differences between a biosimilar and the reference medicine, the most sensitive and thorough analysis need to be applied. Chances of picking up minor molecular differences are increased by using highly sensitive state-of-the-art physicochemical and biological activity analytical procedures whose sensitivity has exponentially increased in the last 10 years. Accordingly, the module that addresses the quality attributes (i.e. the structural and biological activity characterization) is considerably more extensive for biosimilars than for original products (**Figure 1**). Features such as primary and higher order structures, including tertiary conformation, disulphide bonds, aggregate formation, glycopattern, and in-vitro and in-vivo bioactivity, are thoroughly examined and compared. If the head-to-head quality comparability assessment does not reveal a significant divergence between both biological medicines, it is improbable that subsequent comparative Phase III trials will uncover any difference in the light of the magnitude of the inter-patient variability (Weise et al., 2014). Nevertheless, based on the EMA rigorous 'Totality of the Evidence' approach (Weise et al., 2012), confirmatory clinical studies in patients are usually required to mitigate any potential residual risk. Non-clinical and bioequivalence studies, comparative in nature, are also required. Finally, an active post-marketing surveillance plan (pharmacovigilance) also needs to be presented for approval.

Orvieto and Seifer (2016) have recently questioned the biosimilar follitropin clinical comparability trials. They claimed that the indications studied were insufficient, and they raised doubts about the choice of the primary endpoint, and concerns over the potential impact of the minor physicochemical differences. However, they failed to acknowledge that even two consecutive batches of any original biologic are never identical. Furthermore, in the light of the inter-patient variability, performing equivalence trials in additional indications would not have provided any further insights into the similarity of both products, to the far more sensitive comparison of the physicochemical attributes. Biosimilar trials are designed on a case-by-case basis, under the understanding that the objective is not to demonstrate safety and efficacy *per se*, but rather to reconfirm the already demonstrated similarity. Hence, the design of the clinical development programme for biosimilar candidates does not necessarily have to mimic that of original products. Comparable efficacy should be shown by using a primary endpoint resulting from the drug's pharmacological action, in order to discard differences that may not be attributable to the product. Number of oocytes retrieved stands out as the most sensitive endpoint for an accurate comparison of the product's efficacy. Contrarily, ongoing pregnancy rate is often confounded by factors unrelated to FSH action, and should be rather used as a secondary efficacy measure.

Biosimilar rFSH: another follitropin alfa

The specific studies required to demonstrate comparability of a biosimilar candidate versus a reference product may vary qualitatively and quantitatively from case to case. Different biotech drugs differ in their molecular mass, and in their functional and structural complexity. A monoclonal antibody such as rituximab (anti-CD20) would probably fall at the high end of the complexity scale, whereas insulin would be at the low end. The treatment regimen, the indications, the variability of the endpoints, and the expected efficacy-to-safety profile also impact on the nature of the studies needed (e.g. the number of patients required for comparability purposes). Follitropin is a thoroughly characterized protein used in short-term therapy, and has a well-defined pharmacological effect in women – stimulation of ovarian follicle development. Efficacy correlates with this effect. Notwithstanding the difficulties associated with drug development, follitropin's molecular, pharmacological and therapeutic profile allows for a fairly straightforward development of biosimilar candidates. This is reflected in the EMA guidance that lays down the non-clinical and clinical requirements for rHuFSH-containing medicinal products claiming to be similar to another one already marketed (EMA (European Medicines Agency), 2013).

The first biosimilar to Gonal-f®, launched in Europe in 2014, was Bemfola® from Finox Biotech (Rettenbacher et al., 2015). More recently, Ovaleap® (Teva) has become the second biosimilar rFSH being marketed (Strowitzki et al., 2016). The manufacturing conditions of any of the biosimilar versions, their characterization and impurity profile, the specifications and the stability, are all in full compliance with the EMA standards for any biotech product. As mentioned earlier, the burden of the demonstration of similarity relied in both cases on an exhaustive, highly sensitive, molecular comparison to ascertain essentially overlapping physicochemical homology in the fundamental attributes. Products resulting from chemical degradation were equivalent in both medicines, and no concerns over aggregate formation or fragments were highlighted. As for batches of the original reference products, it is not expected that the quality features in the similar biological and the reference medicinal products will be identical, as long as the key attributes are preserved. Notably, variability in post-translational modifications, also occurring among the originator's batches, may be acceptable. Bemfola® and Gonal-f® essentially share the monosaccharide profile, and sialic acid composition. Similar glycan structures are found for the alfa-chain. For the beta-chain, there were glycan differences regarded as minor by evaluators. Those differences were in line with the biosimilarity principle given the inherent batch-to-batch variability of each individual product. Indeed, some of the observed variations are smaller than those allowed for follitropin in the European Pharmacopoeia monograph. As for Ovaleap®, the presence of a higher amount of the sialic acid variety N-glycolyl neuraminic acid (Neu5Gc) was considered acceptable and sufficiently justified. Such minor differences of either biosimilar version versus Gonal-f® had neither an impact on the biological activity – whether compared *in vitro* or *in vivo* – nor on their ability to bind the receptor. Likewise, pharmacokinetic, single-dose and repeat-dose toxicity studies conducted in rats did not reveal any significant difference. Additionally, the relative pharmacokinetic (PK) properties between the biosimilar candidates and the reference product were also determined clinically in Phase I trials in healthy female volunteers. PK bioequivalence was concluded. Likewise, pharmacodynamic parameters were assessed during head-to-head Phase III trials as a complementary measure of comparable efficacy. As expected, comparability between both products was confirmed (Rettenbacher et al., 2015; Strowitzki et al., 2016). Therapeutic equivalence for the primary endpoint (number of oocytes retrieved), and for other relevant secondary endpoints, was consistently established, and overall, the adverse events profile was shown to be comparable. Hence, in the light of the 'Totality of the Evidence', each of the two biosimilar products launched in Europe was considered to be highly similar to the originator rFSH-alfa-bearing medicine, i.e. to share essentially the same API.

Conclusion

In the late 1990s, both doctors and patients rapidly adopted the recombinant versions of FSH (Zwart-van Rijkom et al., 2002). In some instances, this probably led to the sequential administration of the two original recombinant molecules in a given patient, and possibly the switch from urinary to recombinant FSH. In spite of the original products' physicochemical differences, no harmful consequences had been reported as a result of using either, or of reciprocally exchanging them. Moreover, analogous, but non-comparable, original biological medicines have frequently been switched in a given patient on clinical and non-clinical grounds: for instance, diverse anti-TNF antibody products, structurally different erythropoiesis stimulating agents, beta interferons and hormones (Ebbers et al., 2012). No detrimental effects, notably immunogenicity, have been uncovered from switching among such medicines despite the fact that their physicochemical dissimilarities are far wider than those found between biosimilars and their reference medicine. Under these premises, it is no surprise that no increased incidence of adverse events has been registered since the first biosimilar was launched in Europe in 2006, and that no unexpected reactions have arisen from the experience of interchanging reference biologics with their biosimilar counterparts (Kurki et al., 2017). The lack of detrimental consequences was anticipated in view of the rigorous biosimilars regulatory framework set by the EMA. Not all regulatory agencies around the world have adopted such high standards, and some follitropin products that are being approved under less stringent regulatory criteria would probably not make it to the European market, and should probably not qualify as biosimilars.

All in all, experience gained from Europe's leadership in the biosimilars arena is reassuring. The lower investment needed for biosimilar development compared with the original drug, along with increased competition resulting from biosimilars entry into the market, has led to a reduction of the average price of biologic drugs that may contribute to optimizing healthcare expenditure as for the experience gained in other therapeutic areas (Flodmark et al., 2013; Tsao et al., 2014). Treatments such as IVF may also benefit from such trends (Foxon et al., 2015; Ripellino et al., 2015) and, therefore, patient access to infertility care will ultimately improve (Aitken, 2016).

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Declaration: Dr Fauser has been involved in basic science related to human recombinant FSH, as well as the process of product development with almost ALL gonadotrophin-producing companies since the early 1990s, whether originator or biosimilars (Organon, Serono, Ferring, Teva, Finox). Dr de Mora has worked as speaker/consultant for Finox, Sandoz, Roche, Pfizer and other pharmaceutical companies (on biosimilars and biotech drugs in general). In particular, he is consultant for a pharmaceutical organization where Merck Serono is an active participant, and has recently collaborated as a speaker specifically for Merck Serono (November 2016). Transparency reveals that both co-authors have collaborated with producers of original and/or biosimilar rFSH.

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