Commentary

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Journal of Reproductive Endocrinology & Infertility
ISSN 2476-2008

2017
Vol.2 No.1:15

DOI: 10.21767/2476-2008.100015

Commentary on the Orvieto and Seifer Editorial on Biosimilar "rFSH-bearing" Medicines in Reproductive Biology and Endocrinology

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Citation: de Mora F (2017) Commentary on the Orvieto and Seifer Editorial on Biosimilar "rFSH-bearing" Medicines in Reproductive Biology and Endocrinology. J Reproductive Endocrinol Infert 2017, 2:1.

Received date: April 22, 2017; **Accepted date:** May 06, 2017; **Published date:** May 10, 2017

Abstract

The approval of two biosimilar follitropin alfa-bearing medicines triggered a debate among reproduction biology specialists, as to their risk-to-benefit balance. Controversies were discussed by Orvieto and Seifer in their Editorial "Biosimilar FSH preparations-are they identical twins or just siblings?" published in Reproductive Biology and Endocrinology in 2016. This commentary is intended to challenge some of the authors' statements on the clinical uncertainty attributed to biosimilars. Of note, as a key argument, Orvieto and Seifer express their concern over a potential therapeutic impact of existing physicochemical differences between biosimilars and reference products. Put in context, physicochemical variability is intrinsic to any biologically-sourced medicine. Indeed, based on the experience on batch-to-batch heterogeneity of original biomedicines, minor molecular changes in non-essential attributes may be clinically acceptable. Therefore, the stringent science-based comparability exercise between a biosimilar candidate and a reference product is designed to show that those potential minor physicochemical differences do not significantly alter safety and efficacy. Hence, evidence supports that biosimilars, such as Bemfola® and Ovaleap®, and their original counterpart, Gonal-f®, share essentially the same active substance. Physicians and patients should thus be reassured that follitropin alfa-bearing biosimilars approved under the EMA standards provide a high quality alternative to original products.

Keywords: Assisted reproductive technologies (ART); Bemfola; Biosimilar; Follitropin alfa; Gonal-f; Infertility; Interchangeability; Ovaleap; Recombinant human follicle stimulating hormone (rFSH); Similar biological medicine

Commentary

The Orvieto and Seifer Editorial "Biosimilar FSH preparations-are they identical twins or just siblings?" published in Reproductive Biology and Endocrinology (2016) [1], discusses the two first biosimilar medicines containing recombinant follicle-stimulating hormone (rFSH) approved in Europe, and elsewhere: Bemfola® and Ovaleap®. The authors focus on the studies undertaken to demonstrate comparability with the reference original medicinal product, Gonal-f®. However, the arguments used are based on a conceptual misunderstanding of the science behind biosimilars [2]. Our commentary is complementary to the letter from Strowitzki et al. [3], and is intended to reassure reproductive specialists that rFSH biosimilar medicines provide an alternative high quality treatment opportunity.

Orvieto and Seifer (2016), repeatedly state throughout the paper that "biosimilars are not exact copies" of the reference product. This fact should be set in context: the authors fail to acknowledge that even two consecutive batches of any biologic are never identical. Such batch-to-batch variation, expressed in original glycosylated biologics mainly as modifications in the isoform distribution [4], may actually be magnified in biological medicines subject to manufacturing changes. Subtle structural differences between a biosimilar and the corresponding reference originator are therefore expected, and, based on evidence, are therapeutically acceptable. In reproductive medicine for instance, there is substantial isoform heterogeneity among commercial original follicle-stimulating hormone (FSH) products, whether recombinant or urine–derived, with no evidence of a significant divergence in their efficacy and safety profile, as acknowledged by Orvieto et al. [5].

Building on the knowledge gained from studying the inherent heterogeneity of original biologics, the purpose of the biosimilarity exercise is to exclude clinical relevance of those minor differences found in physicochemical attributes [6]. This is achieved by covering three essential milestones by means of a stringent development program: (1) the analysis of several batches of the reference product, to prevent that differences with the biosimilar candidate exceed the intrinsic heterogeneity pattern of the molecule, (2) the laboratory physicochemical and functional analytical comparison, as the most sensitive approach to pick-up even clinically non-significant differences, and (3) the performance of head-to-head trials in patients meant to discard any residual risk. Indeed, comparative phase III trials are in essence confirmatory, since, in the light of the magnitude of the inter-patient variability in response to treatment, clinical

comparability studies would likely not uncover differences undetected during the early analytical stages [7]. Hence, there is no additional value in the context of FSH biosimilarity to checking clinical equivalence for each and every indication of Gonal-f®. Therefore, the Orvieto and Seifer's expressed concerns over the need "to conduct phase III randomized controlled trials (RCT) aiming to demonstrate that those changes do not adversely affect the identity, purity, or potency of the potentially approved biologic product", and "further comparative studies are needed in other patient populations that are encountered during routine daily clinical practice", are not scientifically founded. Therefore, the aim for a biosimilar candidate development is not to demonstrate safety and efficacy per se, but rather to show high similarity. Hence, for that purpose, the design of the clinical development program for biosimilar candidates may not necessarily mimic that of an original product. In the light of this fact, the statement "These studies were underpowered with reference to pregnancy rates" is confounding. Several factors, besides FSH, influence pregnancy rates and live births, but recruitment and growth of ovarian follicles reflect primarily the effect of the hormone in women. Therefore, in assisted reproduction, "number of oocytes retrieved" stands out as the most sensitive endpoint for an accurate comparison of the efficacy of two medicines containing FSH. Oocyte retrieval may reveal product-related differences, and minimize a potential bias introduced by differences rather attributable to patient- or disease-related factors.

On another point, Orvieto and Seifer advise "…against interchanging or substituting innovator and biosimilar agents in clinical practice, and believe that the decision whether to use an innovator or a biosimilar product, should be reserved to the discretion of the treating physician". Few would disagree that, today, precluding substitution among biologics by the pharmacist without the prescriber's consent, should be advised. On the contrary, a switch from an original reference product to its biosimilar counterpart, or vice-versa, under the treating physician's surveillance, i.e. interchanging, as defined in Europe, is normally allowed. However, concerns have been raised over the magnitude of the safety of switching. In the light of the frequently practiced switch between different gonadotrophin preparations in assisted reproduction (so-called mixed FSH protocols), and the switching experience in other therapeutic areas among non-comparable original biologics, there is likely a very low risk associated to a change of prescription between two highly similar products in a given patient [8]. Accordingly, opposite to the author's view that "…most health organizations do not consider biosimilar to be interchangeable with innovator product…", an increasing number of organizations, acknowledge, and, in some cases recommend, that patients being administered the originator medicine, switch to the corresponding biosimilar even for highly complex biologicals used in long-term treatments [9-11].

Conclusions

The EMA paved the way in creating a regulatory framework for the development of biosimilars, whose scientific principles were later essentially reproduced by the World Health Organisation (WHO), and adopted in essence by reference regulatory bodies (including the United States' FDA). The biosimilar concept represents a shift of paradigm, which taken out of context, may raise concerns that could ultimately be detrimental to patients. Physicians and patients should be reassured that follitropin alfa-bearing biosimilars approved under the EMA standards provide a high quality alternative to original products [12]. Biosimilars bear essentially the same active substance as the reference product to which they are equivalent in quality, safety and efficacy, and with which they share the dose, and the route of administration for the same indications. Accordingly, in support of the rigor of the European regulatory framework, since the first biosimilar was launched in 2006, the number of reports on side effects, or on clinical consequences associated to immunogenicity, has not increased. In other words, in Europe there is no evidence of any particular therapeutic risk attributable specifically to the use of a biosimilar versus the originator. Therefore, Orvieto and Seifer's assertion "(Biosimilars products and Gonal f®)… may still differ in strength, purity …" is an unproven claim, and there is no evidence to support that the risk-to-benefit balance of biosimilars exceeds that of original products. Contrarily, as stated by Weise et al. [2], from the EMA, "the risk for detection of new (serious) adverse effects after licensing is considered much lower for a biosimilar than for a biological containing a new or modified active substance" [13].

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This article is available from: 10.21767/2476-2008.100015