Not all new recombinant human erythropoietins are biosimilars


To the Editor: We completely agree with the critical point of view expressed by Dr Singh regarding the new challenges raised by epoetin-z’s copies known as follow-on epoetin.1 However, we would like to stress the point that the qualification of Wepox (Wockhardt Limited, Mumbai, India) as a ‘biosimilar’ is probably not fully correct.

We acknowledge that this epoetin’s copy is a follow-on epoetin (related to US regulatory rules), nevertheless, naming those products as ‘biosimilars’ could bring some confusion and misunderstanding in the European Union (EU). As the patents for epoetin-z have expired recently in the EU and elsewhere, some pharmaceutical manufacturers have started developing copies. The European Medicines Agency (EMEA) has made efforts to establish guidelines2 for the development and approval of biopharmaceuticals through the biosimilar pathway for biotechnology derived proteins (rHu-Epo, G-CSF, …). This pathway is totally different from the regulations for generic chemically defined drugs.3 At this time, three rHu-EPO have been accepted as a biosimilar in the EU by the EMEA after having performed the required phase I and III comparative studies. To the best of our knowledge, Wepox has not fulfilled these requirements. Indeed, according to European biosimilar guidelines for rHu-Epo,4 the clinical efficacy and safety of biosimilar rHu-EPO preparations should be demonstrated in at least two adequately powered, randomized, parallel group clinical trials in comparison to a reference product.5 As mentioned by the author, potential differences between biosimilar glycoproteins such as rHu-EPO and the originator compounds may have differences on immunogenicity, pharmacokinetics, and purity, because of the transgene, the host cell line. The culture conditions and the purification procedures applied by a follow-on manufacturer cannot be the same as the original.

According to the EMEA biosimilar guidelines, extensive comparability testing will be required to demonstrate that the biosimilar has a comparable profile in terms of quality, safety, and efficacy as the reference product (physicochemical and biological properties between production batches (that is, comparability) and in comparison with a reference product (that is, similarity)). Although several assays are available, reliable tests for safety and efficacy still require development and international standards. Clinical trials and postauthorization pharmacovigilance are essential to guarantee the product’s safety and efficacy over time. In consequence, pharmacovigilance, as part of a comprehensive risk management plan, is needed to include regular testing for consistent manufacturing of the drug.

This postauthorization program is an integral part of biosimilar guideline. From our knowledge, Wepox has not been developed in accordance with the EMEA biosimilar guidelines. Therefore, the wording of the authors naming this product as a ‘biosimilar’ could bring some misunderstanding in Europe.

4. EMEA website: http://www.emea.eu.int/index/indexh1.htm (Guidance Documents/Biosimilar Products).

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Response to ‘Not all new recombinant human erythropoietins are biosimilars’


Attaf and Torres suggest that we inappropriately use the term ‘biosimilar’ to describe Wepox in our paper on pure red cell aplasia. They suggest that using the term ‘biosimilar’ to describe Wepox might be confusing in the European Union.1 Further, Attaf and Torres suggest that clinical efficacy and safety studies and postmarketing surveillance should be used to differentiate a biosimilar from a follow-on biologic. Attaf and Torres argue that as Wepox has not undergone the aforenamed studies it cannot be described as a biosimilar to epoetin-z. We humbly disagree. To our knowledge, the terms ‘biosimilar’ and ‘follow-on biologics’ are used interchangeably. Consequently, we believe this is simply an issue of semantics.2,3 Indeed, the European Agency for the Evaluation of Medicinal Products (EMEA) has taken the position that biosimilar medicines are follow-on versions of original biological medicines.4 At this point, it is not possible for us to critically comment on the postmarketing surveillance infrastructure adopted by Wokhardt India (the manufacturers of Wepox) and whether it adheres to EMEA guidelines. Although we agree that the EMEA has been more enlightened than the US Food and Drug Administration in addressing the issues related to biosimilars, especially with respect to epoetin biosimilars, undergoing EMEA regulatory approval should not be a prerequisite for an innovator epoetin molecule to be considered a biosimilar. We believe that ‘the process is product’ concept for biologics remains a matter of controversy. The key...
message is that agents considered as either biosimilars or follow-on biologics should be regarded as essentially different from the innovator biologic by virtue of subtle differences in the manufacturing and/or purification process. These agents must undergo formal regulatory approval and they should be marketed in the context of a strong pharmacovigilance infrastructure. In this regard, the EMEA has provided a well-thought-out process for regulatory approval, and the European Union, like the United States, has robust pharmacovigilance in place.


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Hormone therapy and loss of kidney function


to the editor

To the Editor: We read with interest the stimulating article by Ahmed et al.1 on the association of oral hormone replacement therapy and kidney function in postmenopausal women.

The authors reported the baseline characteristics of the groups by categorical hormone therapy use. There was a significant difference in terms of the use of nonsteroidal anti-inflammatory drugs and diuretics. The groups namely ‘Estrogen only’ (46.8%) and ‘Progestin only’ (52.5%) had a higher percentage of patients on diuretics. The percentage of patients on nonsteroidal anti-inflammatory drugs was higher (45.3%) in the ‘Estrogen only’ group. The elderly (all 66 years old or older) made up the entire data population. This makes the subjects more vulnerable to the effects of both nonsteroidal anti-inflammatory drugs and diuretics on the renal function. Although other factors were analyzed in multivariate analysis, we are surprised that the authors did not include diuretics in the analysis. These drugs are known to affect effective circulating volume and renal function.2,3

Logistic regression analysis has shown the greatest decline of glomerular filtration rate in the ‘Progestin only’ group (Δ, 3.98; confidence interval: −0.30, 8.26) followed by the ‘Estrogen only’ group (Δ, 1.21; confidence interval: 0.28, 2.14), but the ‘Combined group’ had the least decline in glomerular filtration rate (Δ, 0.99; confidence interval: −0.56, 2.54) with large confidence intervals.1 They did not offer a plausible explanation for this discrepancy. We hope that they have a reasonable explanation for this, or is this just a statistical finding? It will be interesting to see their results with the inclusion of diuretic use in the analysis.


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