

## **Biosimilars in Rheumatic Diseases. Position of the Royal Belgian Society of Rheumatology**

*Rene Westhovens MD, PhD president KBVR/SRBR*

*September 2015*

Patents of several biologicals have expired or are close to expiration and follow up versions are being developed and are already marketed or very close to marketing. Biologicals are complex molecules with unique structures made by living organisms and difficult to replicate. Changes in cell lines used to produce them, processes as post-translational glycosylation, might result in similar but not identical products. While this is also the case in reference products over time, due to changing production processes or changes in manufacturing sites, this will be certainly the case with follow up versions (= biosimilars), leading to a potentially altered biological function and different immunogenicity compared to the reference product. This might lead to differences in the efficacy and safety profile. Because biologicals have a tremendous impact on the outcome of most rheumatic diseases, but also the costs associated with them being an increasing issue, the rheumatologists are challenged in their practice. Indeed the first randomized trials are published demonstrating equivalence of biosimilars to reference products in terms of efficacy and safety and this after investigating carefully pharmacokinetics and pharmacodynamics. Meanwhile so called bio-originators also lowered their price in Belgium.

Clinicians will face decisions concerning which product to use and therefore have to understand the inherent differences (or similarities) between the biosimilars and their reference compounds, the regulatory approval processes behind and how this might influence treatment efficacy and safety in their patients, both on short and long term. Because every rheumatologist will recognize the financial burden of treating patients with biologicals, there is of course an evident interest in lowering costs of treatment. Most rheumatologists are however not yet fully aware of the potential differences and of the regulatory definitions and requirements behind these drugs and the KBVR/SRBR will give them updates regularly. Demonstrating biosimilarity is not only demonstrating PK equivalence as in classical generic drugs. The chemistry, manufacturing and control part of the application of a biosimilar is larger than that of the reference product. The non-clinical results should almost be superimposable with the originator and clinical data require demonstration of equivalence in RCT's of sufficient size. An important program of post-marketing surveillance is needed for long-term efficacy and safety assessments, as is the case for reference products. Extrapolation to other diseases than those in which the biosimilar was tested for approval is currently possible from the regulatory perspective. However, this has initiated several discussions and concerns about the risk of under- or overtreatment as well as about safety. Automatic substitution should not be possible in Europe because of the inherent differences and certainly every switch should be the responsibility of the treating physician as he/she needs to carefully follow up eventual impact on efficacy and immunogenicity. This implies also that non-proprietary ("generic") names would best be avoided in prescriptions. In parts of the world with less stringent regulations, "intended copies" that are not adequately characterized are developed. Such products are certainly of danger and in view of an "open world" this needs to be monitored. The ultimate success of biosimilars will depend on the confidence treating physicians will develop in these agents. The KBVR/SRBR will closely follow up the marketing of biosimilars with a permanent independent working group acting in full transparency as an intermediate also with the industry, regulatory authorities and government. Current members are Rik Joos, Patrick Durez, Filip van den Bosch, Pierre de Marneffe and Rene Westhovens.

In the presentation at the 18<sup>th</sup> Belgian Congress of Rheumatology 2014 our viewpoint was discussed with all members of the KBVR/SRBR and this was the start of a continuous reflection on this topic, guiding the practicing rheumatologists through a changing world. The group is also aware of

discussions within the patient organisations on his topic and will seek contact with them to have an open discussion. We currently support the statements of the FAGG/AFPMS in Belgium on the biosimilar topic:

- After approval, the safety of biosimilars needs continuous monitoring (risk management plan and adequate pharmacovigilance)
- Biosimilars can be immunogenic which might effect efficacy and safety. This can not be predicted on non-clinical studies and needs permanent vigilance and follow up in large patient groups on the long term. Immunogenicity can not be extrapolated from data of the reference product.
- Specificity in identification of biotechnological medicinal products is important when reporting adverse events.
- Biosimilars will have data of comparison with the reference product but there is currently no comparability between biosimilars. Also regarding efficacy: switching a biological to a biosimilar or vice versa is not evident and a different issue compared to starting a new patient on such a drug.
- Biological medicinal products are in general not interchangeable in view of their complexity and prescription by INN (International Non-proprietary Name) is not recommended. If prescriber switches from one to another (original to biosimilar, biosimilar to original or biosimilar to biosimilar) he must monitor his accurately.  
By this, VOS (voorschrijven op stofnaam)/DCI (prescription en dénomination commune internationale) is not recommended.

Additionally our working group would also like to highlight that cost responsibility for the use of biological medicines is important in order to provide optimal care for as many patients as needed. This would also imply that even with lower costs of a drug, a careful evaluation of individual indications and safety risk remains mandatory. This is a key responsibility for rheumatologists.

Individual patients under perfect disease control should not be forced to change product only because of cost saving reasons. One should also make a distinction between new indications and patients on effective long term treatment. One should be aware that individual patients might react differently on a similar product. At the end rheumatologists are responsible and need to be able to make the best choice for and in agreement with every individual patient also concerning the way of administration.

In complex pathologies (e.g. dermatological/rheumatological or rheumatological/gastroenterological) the treating physician needs to weigh carefully the different options for optimal care, as scientific data of a biosimilar in one disease can not automatically be transferred to another disease.

While every rheumatologist has the end-responsibility for appropriate patient care, the rheumatological community needs to collaborate on gathering additional data on outstanding issues.

References:

Yoo DH, Hrycaj P, Miranda P et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis.* 2013 Oct;72(10):1613-20

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