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VIEWPOINT

Biosimilars: what do patients need to consider?

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INTRODUCTION

The end of an exclusive patent period is a major reason for the development of a highly similar version (biosimilar) of an original authorised biologic, and is associated with the advantage of a cheaper available compound. When a biosimilar is approved by the FDA and/or EMA, any differences with the reference biologic will have shown not to affect safety or effectiveness. The guiding principle for physicians has been – and still is – that the patient's well-being is the primary consideration whatever the intervention or the drug employed. PRIMUM NON NOCERE is the Latin aphorism for “first do no harm” and is the preeminent issue to be considered.

On the other hand, when released on the market, the pharmacological and pharmacokinetic aspects of a biosimilar will have been tested following the same rigorous regulatory assessments as all available bio-pharmaceuticals. Randomised clinical trials test also the effectiveness. However, several important issues related to the practical management – like the pharmacovigilance, switching, interchangeability or substitution of biologics with their biosimilars – still need to be assessed and continuously updated. They are causes of anxiety and scepticism among people with rheumatic and musculoskeletal diseases.

The position paper here, realised by the EULAR-PARE patient community, opens the discussion about some relevant issues. The recent EULAR recommendations have already considered the position of the first biosimilar for the treatment of rheumatoid arthritis. However, with the availability of more evidence-based data, reliable codes of practice and general recommendations are planned for the medical and patient community.

Of course, as a federation of scientific, patient and health professional societies from 45 different countries, EULAR cannot release detailed recommendations on biosimilars applicable in all countries, but just a point of view in agreement with the major regulatory agencies such as EMA, FDA and WHO.

Professor Maurizio Cutolo, EULAR past president

ABSTRACT

A view from the EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (SCPARE) on some of the issues that patients might wish to consider about biosimilars in shared decision-making discussions with their rheumatologist. The paper also points to the need for more information on biosimilars being made available in lay language.

More than 120 million people are living with rheumatic and musculoskeletal diseases (RMDs) in the European Union today. Access to safe, effective and affordable medicine is of paramount importance to them. In recent years, the development and introduction of biological medicines (biologics) have vastly improved the treatment of some diseases, and enabled many people with RMDs to enjoy a much better quality of life.

These original biologics are beginning to reach the end of their exclusive patent period.

Manufacturers are therefore using the opportunity to develop highly similar versions of the original authorised biologics called biosimilar medicines (biosimilars). There is an opportunity for these biosimilars to be available at a lower cost than the original medicines, possibly making them more widely accessible to patients and offering more treatment options to physicians. The EULAR Standing Committee of People with Arthritis/Rheumatism in Europe (EULAR SCPARE) welcomes these new possibilities for increased choice of treatment and for patients to manage their disease more effectively.

However, in common with the introduction of all new medicines, biosimilars have raised a number of questions and concerns in the minds of patients, ranging from the approval process to safety and risk. In addition, in the context of the national member organisations of EULAR, patients and patient organisations are keen to understand EULAR's own



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position on biosimilars. The EULAR SCPARE has therefore produced the following paper, which incorporates some of the questions being asked now, and points to what is still needed to assist patients in their understanding and assessment of biosimilars in the context of making informed decisions.

WHAT IS A BIOSIMILAR?

The European Medicines Agency (EMA) describes a biosimilar as follows:

A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines. The active substance of a **biosimilar** and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the **biosimilar** has a degree of natural variability. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.¹

This description by the EMA, while seemingly straightforward, has prompted patients to ask some of the following questions about biosimilars and their use in clinical practice for the treatment of RMDs.

APPROVAL: WHO REGULATES BIOSIMILARS?

The EU was the first region in the world to set up a legal framework and a regulatory pathway for biosimilars.² They are by law reviewed centrally by the EMA and they have to follow the general scientific guidelines related to biological medicines and undergo the same rigorous regulatory assessment by the relevant regulatory authorities as must all other biopharmaceuticals. The European Commission issues the 'Decisions' concerning the authorisation of these medicinal products on the basis of the scientific opinions from the EMA. The resulting marketing authorisation is valid in all EU Member States. The first biosimilar was approved by the European Commission in 2006, so they are not new.

If the reference medicine has been authorised in the EU for several years, and its clinical benefit is established, "some studies carried out with the reference medicine may not need to be reproduced" for the biosimilar.¹ Patients have commented that this has allowed approval of biosimilars after only very short or limited trials without sufficient time to consider any longer term effects of the medicine. In addition, EU laws/regulations allow for 'extrapolation' of biosimilars, meaning that comparability studies in the context of one disease can be transferred to other indications without having to carry out any additional studies before approval. Patients wish to know what level of risk this presents to them. To counter patient concerns on this point, the EMA is

developing criteria (EMA/129698/2012 and EMA 184035/2013), but what happens at present is unclear to patients.

In the wider context, in 2010, the WHO published its Guidelines on Evaluation of Similar Biotechnological Products.³ These guidelines aim to provide a set of globally acceptable principles to approve biosimilars that would assure quality, safety and efficacy. However, in the meantime, before all these principles are firmly in place, the possibility of cross-border availability of biosimilars from countries with differing approval regimes has also sparked patients' concerns.

VARIABILITY: WHAT DOES THIS MEAN FOR PATIENTS?

The active substance of a biosimilar must be similar, in molecular and biological terms, to the active substance of the reference biological. However, both consist of complex molecules that are made using living organisms. Owing to this inherent complexity and batch-to-batch variation of biologics, varying degrees of biosimilarity exist. For patients, this is an important point. Despite the European Commission assurance that "a biosimilar ... and its reference medicinal product are expected to have the same safety and efficacy profile",⁴ and the EMA statement that "the amino acid sequence is expected to be the same",¹ questions remain in patients' minds about whether this variability might carry additional risk. Will biosimilars increase immunogenicity? Will side effects be the same as the reference biologic?

SAFETY: WHAT CONCERNS PATIENTS?

Being able to rely on the safety of biosimilars is paramount for patients and patients' organisations. Safety includes a broad range of issues including pharmacovigilance and how to assess risk.

PHARMACOVIGILANCE: WHO IS MONITORING BIOSIMILARS?

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem."⁵ The aim of pharmacovigilance is to enhance patient care and patient safety, and to provide reliable, balanced information for the effective assessment of the risk-benefit profile of medicines. Patients therefore need to know how to access this information and how, to whom, and by whom, suspected adverse effects are reported. Under the EU pharmacovigilance legislation, patients themselves can report suspected side effects directly to the national authorities.⁶ It is important therefore for patients to be able to determine which national public health institution authorises, tracks and monitors medicines in their country. Patients outside the EU will need to satisfy themselves about the laws/regulations/pathways for biosimilars in their own

countries, and as to what systems of pharmacovigilance are in place.

As required by EU law, every medicine must have either the invented (trade) name, or the name of the active substance together with the company name/trademark. For biosimilars, because of their special characteristics, the brand name should be used and not the International non-proprietary name.⁷ This is important for clear identification and traceability to support adverse drug reaction reporting, and for monitoring safe use. Some patients have pointed out that to be able to correctly identify the biological being prescribed for them, physicians must ensure that the brand name always appears explicitly on the prescription.

RISK: SWITCHING, INTERCHANGEABILITY AND SUBSTITUTION

All patients with RMD accept that all treatments and medicines carry some risk, as does the disease itself. However, central to decision-making is calculating what risk is acceptable. Patients can only make informed decisions and choices about their treatments if they have access to reliable information and facts.

Many patients consider that leaving open the possibility of *switching* (transitioning between the reference product and the biosimilar) without the consent of the patient, *interchangeability* (going back and forth between the reference product and the biosimilar with the expectation of achieving the same outcome) without the knowledge/consent of the patient, and *substitution* (the practice of dispensing one medicine instead of another equivalent) without the knowledge of the prescribing physician and the patient, would introduce unacceptable uncertainties into that decision-making process. The EMA makes no recommendations on whether a biosimilar should be used interchangeably with its reference medicine.⁸ So there is no certainty that it will not take place. Substitution policies are within the remit of the EU member states.

People with RMDs must at all times be fully aware of the medications that they are taking. Urgently needed are clear codes of practice, written in lay language, and drawn up with the involvement of patients. As for all medicines, patients need to be able to make fully informed decisions about whether to take a biologic or biosimilar. They have to be able to assess risk against benefit accurately, and they need the tools to be able to discuss the pros and cons with their healthcare team.

AVAILABILITY

While in general it is expected that biosimilars will be introduced to the market at a lower price than their originator reference medicine, price is determined through market forces, by national competent authorities and competition between originators and the biosimilars manufacturers. This has led to patients' anxiety that the availability of lower-priced biosimilars may increase pressure on clinicians, by health providers and insurers, to prescribe the newer alternative on the basis of cost alone.

While appreciating the realities of economic pressure on health services and insurers across Europe, patients strongly believe that decisions about prescribing biosimilars should be made on clinical grounds and not solely on financial grounds.

WHAT HAS EULAR SAID ABOUT BIOSIMILARS?

In its paper, "EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update", EULAR noted that tumour necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and **biosimilars**), abatacept, tocilizumab and, under certain circumstances, rituximab, are essentially considered to have similar efficacy and safety. When speaking of TNF inhibitors in its recommendations, EULAR listed the five presently approved agents (above) and decided also to mention biosimilars under the proviso that they become approved in the USA and/or Europe; bs-infliximab has recently been approved by the EMA. In particular, it was commented that "current data suggest that at least one biosimilar, CT-P13, has a similar efficacy and safety profile to the original antibody, infliximab, in RA and axial spondyloarthritis."⁹⁻¹⁴

WHAT IS THE POSITION OF EULAR NATIONAL MEMBER ORGANISATIONS?

Some EULAR national patient organisations have already taken the initiative to produce position papers for the benefit of their members raising some of the issues mentioned above. Three examples are:

Cyprus	Cyprus League Against Rheumatism "The 10 Commandments of access to biological treatments" http://www.rheumatism.org.cy/userfiles/theseis%20ASK%20gia%20ta%20biosimilar.pdf Available in Greek only
Germany	"Positionierung der Deutschen Rheuma-Liga Bundesverband eV zur Einführung von Biosimilars in Deutschland" https://www.rheuma-liga.de/biosimilars/
UK	"National Rheumatoid Arthritis Society (NRAS) position paper on biosimilar medicines" http://www.nras.org.uk/data/files/About%20RA/How%20is%20RA%20managed/NRAS%20Biosimilars%20Position%20Paper%20Final.pdf "The Introduction of Biosimilars—Uncharted Waters? Report from a Stakeholder Event held on 9 April 2014 at the Royal College of Physicians, London" http://www.nras.org.uk/data/files/About%20RA/How%20is%20RA%20managed/NRAS%20Biosimilars%20Report.pdf

Cyprus	“Cyprus Rheumatology Society: Position statement on the use of biosimilars in rheumatic diseases” http://www.rheumatism.org.cy/userfiles/FINAL%20Rheuma%20Position%20Statement_GREEK.28-08-.pdf
Portugal	“The Portuguese Society of Rheumatology position paper on the use of biosimilars” http://www.ncbi.nlm.nih.gov/pubmed/24811463
Spain	“Documento de posicionamiento de la Sociedad Española de Reumatología (SER) sobre farmacos biosimilares” http://www.ser.es/actualidad/noticias/documento-de-posicionamiento-de-la-ser-sobre-farmacos-biosimilares/1842 Available in Spanish and English

In addition, the Cyprus Rheumatology Society, the Portuguese Society of Rheumatology and the Spanish Society of Rheumatology have produced national papers about biosimilars:

WHAT IS STILL NEEDED?

The availability of reliable, up-to-date information about biosimilars is crucial to the patient's understanding of biosimilars. Patients and patient organisations need evidence-based information that allows them to make informed decisions and choices about treatment and patient care. Never is this more important than when new medicines are being introduced. The science of biosimilars and their introduction is not straightforward for the lay person to understand. Consequently, questions arise and the implications of treatment by biosimilars have attracted a certain amount of anxiety and scepticism among the patient community.

The Standing Committee of People with Arthritis/Rheumatism in Europe therefore hopes that the scientific community of EULAR will make available to patients with RMD timely lay summaries of all results of relevant and important studies, trials and reviews involving biosimilars. As more evidence-based data on biosimilars become available, reliable codes of practice, recommendations and points to consider developed by EULAR would also be highly appreciated by the European patient with RMD community and help to build confidence and widen their understanding of the use of biosimilars for the treatment of RMDs.

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