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Position statement of the Portuguese Society of Nephrology on the clinical use of biotechnological drugs in renal patients

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BIOTECHNOLOGICAL DRUGS

The last few years have witnessed an exponential growth in the biotechnology industry which is reflected in the availability of more than one hundred biotechnology molecules in several therapeutic areas[1].

There are critical differences between biotechnological and the more common chemical drugs. A chemical drug is a small molecule produced by chemical synthesis with a very well-defined and stable structure, not or barely sensitive to process changes, which is relatively stable. A biotechnological drug or a biopharmaceutical product is a large complex biomolecule with a heterogeneous structure, extremely sensitive to process changes and prepared by the use of living systems, such as organisms, tissue cultures or cells, with the large majority manufactured using recombinant DNA technology. This means that a human gene capable of triggering the production of a specific protein is inserted into a living organism and cultured in the laboratory. The organism incorporates the gene into its cell structure and produces large quantities of the desired protein.

This process of producing proteins in living organisms is definitely more complex than that associated with chemical synthesis. This makes quality control and final product standardisation much more difficult to achieve. Small changes in the process or any type of contamination may permanently compromise the final product. Moreover, and because it is a relatively recent technology, it is even more difficult to find satisfactory monitoring and evaluation methods[2,3].

Regarding protein synthesis, one of the most important issues is related to glycosylation, since this process can influence solubility, degradation and immunogenicity of recombinant proteins[1]. Changes in degradation can produce novel antigenic epitopes not found in the parent molecule, with potentially increased immunogenicity[4] and biological activity. Metabolic half-life may also be affected[5].

During manufacturing, another important concern is microbial or viral contamination, as well the incorporation of impurities such as endotoxins or denatured proteins, for example. These can change the immunogenicity of a biopharmaceutical, including "erroneous" activation of T and B cells and induce an immune response[1].

Analytical studies have revealed the extent of heterogeneity of biopharmaceuticals produced by different manufacturing processes around the world. Variation is illustrated by a number of studies of innovator and non-innovator versions of recombinant human EPO (rHuEPO). Key differences have been found in the structure, stability, composition, concentration and activity of manufactured epoetins. Huub Schellekens has recently published a detailed review highlighting the main issues with biosimilars, with special focus on rHuEPO[6].

A wide range of licenced biosimilars are available in several countries, including China, India and South Korea. Examples of such marketed products include interleukins, interferons, erythropoietins, growth factors, hormones, enzymes and monoclonal antibodies. By contrast, there are considerably fewer biosimilars in the European market[7].

In this paper, we will specifically focus on similarity between biological medicinal products containing recombinant erythropoietins, and address major concerns on interchangeability between originators or between originators and their biosimilar counterparts.

BIOSIMILARS

Recombinant proteins are large molecules which have a highly complex three-dimensional structure and are not synthesised *in vitro*, but produced and secreted by genetically modified cells. During this process, proteins can undergo posttranslational modifications, such as glycosylation, that lead to heterogeneity. Manufacturing and formulation of protein products is thus highly complex, and the manufacturing process is critical to defining the characteristics of the final product. Biological medicinal products are usually difficult to characterise, and past experience has shown that seemingly minor differences can have important clinical consequences. For all these reasons, "copies" of biopharmaceuticals cannot be identical to the original product but, at best, similar.

In Europe, this has been fully acknowledged by the European Agency for the Evaluation of Medicinal Products (EMEA), and is reflected in the fact that these products are called *biosimilars*, and not generics or biogenerics (in the USA, the FDA called them *follow-on biologics*). It becomes important to note what EMEA has stated in their guideline on biosimilars[8]:

"*It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established.*"

As a direct consequence, the approval process that is followed for generic drugs cannot be applied to drugs claiming similarity to biopharmaceuticals. This has been recognised by the Committee for Medicinal Products for Human Use (CHMP) which has developed specific guidelines for similar biological medicinal products containing biotechnology-derived proteins as active substance as well as defined specific guidance relating to biosimilar epoetins[9].

This particular guidance is effective from July 2006 and lays down the non-clinical and clinical requirements for EPO-containing medicinal products claiming to be similar to another one already marketed.

This guidance starts by highlighting the following: "*All epoetins in clinical use have a similar amino acid sequence as endogenous erythropoietin but differ in the glycosylation pattern. Glycosylation influences pharmacokinetics and may affect efficacy and safety, particularly immunogenicity*".

EMEA guidelines mention non-clinical issues such as the manufacturing process and quality control[10]:

"...the safety/efficacy profile of these products [biosimilars] is highly dependent on the robustness and the monitoring of quality aspects... The 'similar biological medicinal products' approach, based on a comparability exercise, will then have to be followed."

Reflecting its greater molecular complexity and recent clinical history (*i.e.* Ab-mediated PRCA), the regulatory requirements are stricter for EPO than for the other recombinant proteins[6].

Based on the assumption that "*sensitivity to the effects of epoetin is higher in erythropoietin-deficient than non erythropoietin deficient conditions*", this document recommends, *that "patients with renal anaemia should be the target study population"*. Regarding characteristics of clinical trials, these guidelines state[10]: *"Comparable clinical efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomised, parallel group clinical trials"*. Furthermore, "*the clinical trials should include a 'correction phase' study during anaemia correction and a 'maintenance phase' study in patients on epoetin maintenance therapy"*. Therapeutic equivalence must

be demonstrated for both predialysis and haemodialysis CKD patients, and by the intravenous as well as the subcutaneous route of administration. At least 12 months of immunogenicity data should be provided.

So, due to the difficulties in establishing equivalence of biopharmaceutical agents, the EMEA approval process is based on '*comparability*': the demonstration of comparable efficacy and safety to a reference product in a relevant patient population. The question of what exactly is to be considered '*comparable*' is not defined *a priori*, and the approval process is likely to vary between products according to the nature and quantity of data available[1].

With regard to the implementation of EMEA guidelines, the Expert Panel still has some concerns, especially related to parameters and equivalence margin, dimension and follow-up period of the clinical studies conducted and the type of patients included.

PHARMACOVIGILANCE

It is recognised that small differences in the cell line, the manufacturing process or the surrounding environment are difficult to determine due to the low sensitivity of existing analytical tests[3]. These small changes have a direct influence on product efficacy and safety, increasing health concerns associated with interchangeability and substitution, particularly in patients receiving chronic treatments[11].

The complexity of the structure of biotechnology medicines and of their production process, the existing small clinical experience with some of these products, and the absent comparative evaluation between originators or ill-defined comparative evaluation between originators and their biosimilar counterparts, imply a more cautious utilisation to guarantee patient safety. The implementation of pharmacovigilance programmes is here a matter of major relevance.

The use of the International Non-proprietary Name (INN) is an issue regarding biosimilars, whereby drugs with the same active ingredient (irrespective of their production process) are given the same name. This can easily lead to inadvertent substitution without the doctor or patient being aware of it. That an independent non-proprietary naming system for biotechnological substances might be needed is being debated within the international medical and pharmaceutical community. Furthermore, although the INN is a useful tool in the context of global pharmacovigilance, other available tools should be employed, such as lot number, manufacturer and other relevant information, as means of product identification[12].

According to Declerck, four issues should be taken into consideration in order to assure more effective pharmacovigilance[11]:

- The biosimilar must have a different brand name;
- For the purposes of the Summary of Product Characteristics (SPC) and patient information leaflet, the active substance of one brand should not be considered identical to that of another brand, given the different production and formulation processes;
- Prescribing based on active substance name should be prohibited for biologics and should be based exclusively on the unique brand (including the route of administration);
- There should be routine use of traceability systems, for example using a barcode.

An unwanted immunogenicity is expected after treatment with non-human proteins, especially when administered repeatedly. Unfortunately, the immunogenicity of biosimilars often cannot be fully predicted using preclinical studies. Therefore, clinical immunogenicity studies are required before approval. The immunogenicity is influenced by several factors, namely patient's genetics and immunological status, type of disease and the product specificities. Even assuming that a biosimilar has the same structure, host cell line, vector and purification methods, it is not guaranteed that its immunogenicity is the same as the original product[13,14]. Therefore, safety data will be needed before marketing authorisation and will also be required post marketing.

The implementation of a pharmacovigilance plan can be a condition for EMEA to approve a biosimilar product. The applicant's ability to convince the Agency that a suitable pharmacovigilance plan will

be implemented can be relevant, although the criteria of what constitutes an acceptable pharmacovigilance plan remain to be determined[12].

Regarding erythropoietins the main issue is the induction of neutralising antibodies resulting in pure red cell aplasia (PRCA)[13]. Considering this serious (although rare) adverse effect, the EMEA guidelines emphasise the need for pharmacovigilance and immunogenicity testing programmes for all biotechnological products.

INTERCHANGEABILITY AND SUBSTITUTABILITY

No solid scientific ground guarantees the safe interchange between any biological medicine, whether originator or biosimilar. These issues are related not only to safety, but also to efficacy and response, since the equivalence between originators is not established, and with regard to biosimilars, neither the equivalence limits nor the definition of "similar" itself are clear.

These particularities of biopharmaceutical products lead to the possibility of clinical harm, which is a major concern if substitution occurs without the knowledge of the prescribing physician. Automatic substitution may affect pharmacovigilance, jeopardising the identification of the brand or manufacturer of the biopharmaceuticals.

Several countries, such as France, the Netherlands, Germany, Italy, Spain, UK and Sweden, for example, have adopted legislation prohibiting the automatic substitution of biological products[6,12].

CONCLUSIONS

Biopharmaceutical agents represent a new challenge in the field of therapy. With regard to biosimilars, these products can be an attractive option in terms of costs and health-economic evaluation. However, it is crucial that the decision for the use of biotechnological drugs should be well supported by high quality and relevant scientific data. Patients, health professionals, health providers, the pharmaceutical industry, regulators, and policy-makers should understand the complexity that surrounds biotechnological drug production and utilisation, and in particular the questions related to pharmacovigilance.

An informed decision is mandatory and implies an adequate knowledge by the physician in order to balance advantages and disadvantages in each specific situation.

Currently, the need for changes in nomenclature procedures and effective pharmacovigilance systems are outstanding issues. At this point, interchangeability, either between originators or between originators and their biosimilar counterparts should be vigorously discouraged.

The Expert Panel of the Portuguese Society of Nephrology believes that the safeguard of therapeutic value and safety aspects are mandatory, particularly in biotechnology drugs prescribed for long periods of time. The Panel also believes there is no absolutely safe interchangeability of bioproducts, and that if changes are required this must in all instances be decided by a medical doctor based on solid scientific and clinical data. In this area, financial issues shall on no occasion introduce additional risks to the patient or overcome medical prescription.

Conflict of interest statements:

Drs. António Vaz Carneiro, António Cabrita, Fernando Macário, Pedro Neves, Fernando Nolasco, Helena Sá: none declared.

Prof. Henrique Luz-Rodrigues has received consultancy fees from Amgen, Janssen-Cilag and Roche.

Dr. Fernando Carrera has received honoraria and lecture fees from Amgen (Europe), Roche (International), Shire (International), Takeda (Europe), and Vifor (International).

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Dr. José Vinhas has received lecture fees from Amgen and Roche, and consultancy fees from Abbott, Amgen, Janssen-Cilag, Roche and Shire. Dr. José Vinhas receives fees from Fresenius Medical Care.

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