REVIEW ARTICLE

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What do nephrologists need to know about biosimilars?

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ABSTRACT

Biotechnology medicines have already helped millions of people to combat diseases which were seen as incurable in the previous era of conventional chemical drugs. Erythropoiesis stimulating agents have revolutionised the treatment of anaemia which develops during chronic kidney disease. Biotech drugs are generally safe and well-tolerated. There are, however, issues which are unique to biologics, such as immunogenicity, and nephrologists have learned much from a recent outbreak of pure red cell aplasia (PRCA) which most probably occurred after only a slight modification of drug formulation of one of the recombinant erythropoietins. The expiry of patent protection for many original biotech drugs has led to the development of products known as biosimilars or follow-on-biologics. The first drugs that attempt to copy original biotech medicines have recently been approved in the European Union. Despite that, there are still uncertainties over the approval pathway for biosimilars, including the required safety data. This review provides an introduction to this new issue, revealing the differences between biosimilars and traditional chemical generics as well as potential problems including safety, pharmacovigilance, automatic substitution, naming, labelling and prescription rules.

Key-Words:
Biotechnology; biotech medicines; erythropoiesis stimulating agents; biosimilars; immunogenicity; pharmacovigilance.

BIOTECHNOLOGY MEDICINES

Biotechnological medicines are polypeptide or protein drugs produced by splicing genes into living organisms such as bacteria, viruses, yeasts and animal or plant cells[1]. These technologies have led to the production of such widely used medicines as recombinant insulin, human growth hormone, clotting factors and erythropoietin. Another type of biotech medicines is a fully laboratory-designed and synthesised version of an endogenous human or animal protein, e.g. monoclonal antibodies. The latest generation of biotech products used in medicine include antisense drugs that interfere with the communication process which makes the cells produce an unwanted protein, e.g. recently approved antisense oligonucleotide for the treatment of CMV retinitis in HIV-infected patients[2].

There are fundamental differences in the structure and biological effects of biologics and conventional chemical drugs[1,3]. Although chemical and biotechnological drugs are all pharmaceutical products, they are completely different in terms of their manufacture, structure and action. Biotech medicines are made from living cells and chemical medicines are made from chemical processes. The molecular structure of biologics is much more complex and their molecular weight could be 100 - 1000 times higher than chemical agents. This difference is best reflected by the molecular weight of a biologic - interferon beta, which is 19 000 D, and aspirin which is 180 D[4]. The complexity of the structure of a protein is also dependent on the unique properties of the protein which forms three dimensional conformations and

numbers of specific interactions with other proteins and receptors ('quaternary' protein structure). The pharmacodynamic properties of chemical and biologic medicines are dependent on the target process or processes they interact with. Whereas chemical drugs usually interact with one or more processes in the organism, biotech medicines interact with many different genes (e.g. interferon gamma interacts with more than 40 genes). Thus the full action mechanism of biological agents is very difficult to characterise and understand[5]. It is relatively easy to map and reproduce the pathways to manufacture a chemical drug where there are no chemical formulae which could be used to delineate the structure of a biotech medicine and the way it is synthesised. In most cases the final product is a mixture of related molecules, e.g. recombinant human erythropoietin contains in a vial or syringe a mixture of several isoforms whose carbohydrate chain content and number of sialic acid residues differ[1,6,7]. Most biologics are also given by parenteral routes or inhaled and the final product is very sensitive to changes in physical parameters (temperature, freezing, sunlight, etc) and requires very stable and well-controlled storage conditions.

The characteristics of the culture of the living organism (line of cells which are all cloned from a single cell) which is used to produce a drug is a key issue in the manufacturing process of a biotech medicine[1,3,5]. Each manufacturer's cell line is unique. The cell line is constructed using a unique proprietary DNA expression vector. The characteristics of incorporation of the DNA are also unique for each cell[5]. The cell line is precisely evaluated for product integrity, activity and overall quality. In addition to product quality, the cell line is chosen based on expected performance in manufacturing such as growth and viability. Therefore each line of cells, bacteria, and yeasts has unique characteristics, and even minor variations could produce different products. The process is also extremely sensitive to changes in both manufacturing and production[5-7]. Despite sophisticated purification procedures, the final product also contains trace impurities specific for different cells (bacteria, yeasts, human, animal or plant cells) used in the production of biotech products[5]. This is important with regard to potential immunogenicity of the final product, which could be facilitated by the foreign protein content.

It is now quite obvious to the practising physician that biotech medicines have extended our capabilities to fight diseases which were considered incurable in the previous era of traditional chemical drugs. The best examples are inherited enzyme deficiencies, i.e. "orphan" diseases and renal anaemia which was always blood transfusion-dependent in the pre-epoetin era[1,8]. Most biotech medicines replace or supplement natural proteins. Most of the 125 biotech medicines which have been approved so far in the US are cytokines, hormones, clotting factors, monoclonal antibodies, vaccines and molecules used for cell/tissue – based therapies[8]. It is estimated that hundreds of millions of patients worldwide have already been helped by biotech medicines. By 2010, biopharmaceuticals will represent 50% of the drug market in contrast to less than 20% in 2004. According to the 2006 Pharmaceutical Research and Manufacturers of America (PhRMA) Survey[8], 418 new biopharmaceuticals are being developed in almost all areas of modern medicine but most for cancer (210), infectious (50) and autoimmune diseases (44), AIDS (22), neurologic (17) and respiratory (13) disorders[4].

WHAT ARE BIOSIMILARS?

The patent protection for the first generation of biotech medicines has already expired or is due to expire in the next few years (Table I). As was the case with conventional drugs, this may lead to the development of drugs attempting to copy the original molecule. In the case of biotech medicines these new drugs have been named "biosimilars"[1,9]. This name is generally used in the European Union while in the US they are called "follow-on-biologics". Due to the fundamental differences in terms of synthesis, manufacturing, structure and function of chemical drugs and biologics, biosimilars should never be called "generics" or "biogenerics"[9]. When talking about biosimilars, every physician has first to realise that these drugs are not exact copies of the existing biological medicinal products or protein drugs but attempted copies. This is because biosimilars are made with a different cell-line and a different manufacturing and purification process, and therefore the final product could not be identical. As mentioned above, chemical drugs are relatively easy to reproduce since their structure is precisely defined. The unique multi-dimensional structure of the polypeptides and proteins and thereby their biological effects are never fully reproducible. In fact, biotech medicines

Table I

Expiry of patent protection for original biotech medicines in Europe and the United States. Modified from: Schellekens H. Trends Biotechnol 2004; 22: 406-416

Company	Product	Clinical indication	US patent expiration	EU patent expiration
Genentech	Nutropin	Growth disorders	Expired	Expired
Abbott	Abbokinase	Ischaemic events	Expired	Expired
Eli Lilly	Humulin	Diabetes mellitus	Expired	Expired
Genzyme	Ceredase	Gaucher disease	Expired	Expired
AstraZeneca	Streptase	Ischaemic events	Expired	Expired
Biogen Roche	Intron A	Hepatitis B and C	Expired	Expired France, 2007 Italy
Serono	Serostim	AIDS wasting	Expired	N/A
Eli Lilly	Humatrope	Growth disorders	Expired	N/A
Amgen	Epogen, Procrit, Eprex	Anaemia	2013	Expired (2004)
Roche	Neorecormon	Anaemia	N/A	Expired (2005)
Genentech	TNKase	Acute MI	Expired (2005)	Expired (2005)
InterMune	Actimmune	Chronic granulomatous disease	2012	Expired (2004)
Genentech	Activase	Acute MI	2010	Expired (2005)
Chiron	Proleukin	HIV	2012	Expired (2005)
Amgen	Neupogen	Anaemia, leukaemia, neutropaenia	2015	Expired (2006)

even with the same molecular weight and synthesised by the same sort of cells or microorganisms could possess different pharmacokinetic and pharmacodynamic properties. This is the case with numerous epoetins alfa which come from different manufacturers outside the European Union and the United States without respecting the innovator rights[6,9]. Such biotech medicines cannot, however, be called biosimilars because they do not meet the regulatory approval standards.

DO BIOSIMILARS ALREADY EXIST?

The first two biosimilars entered the market in 2006 after having been approved by the European Agency for the Evaluation of Medicinal Products (EMEA). Those biosimilar products are Omnitrope (biosimilar to Genotropin) and Valtropin (biosimilar to Humatrope)[10,11].

It is of note that the third application for a biosimilar has just been rejected by the European Medicinal Agency (EMEA)[12]. The application was for an injectable Alpheon, a product which was claimed to be biosimilar to Roferon-A and was therefore intended for the treatment of hepatitis C. The Agency concluded that although the product appeared to be similar during the clinical studies there were significant differences including more side-effects and relapses of the disease compared to a reference product. There was also not sufficient evidence whether the drug might trigger an immunological response – the formation of antibodies. Other biosimilar products are currently under development for the European market by a number of companies. It is expected that more biosimilars will reach the market in the next few years.

WHAT IS THE CURRENT LEGAL AND REGULATORY FRAMEWORK FOR BIOSIMILARS?

The first recommendation for the approval of biogenerics was issued in 2004 by the European Parliament (European Directive 2004/27/EC) and that initiative was followed by the 2005 EMEA Guidelines (EMEA/CHMP/42832/2005). It is clear that these guidelines are still preliminary and subject to changes since the issue of biosimilars is very new, and experience with their use has so far been very limited[3,14].

The Guidelines are divided into two parts. The general part applies to all biosimilars and the second

part contains the annexes for specific products including recombinant human erythropoietin, recombinant human G-CSF, recombinant human insulin and growth hormone[14,15]. It is expected that more annexes referring to other specific products will be issued in the near future.

The guidelines emphasise the problem of the complexity of biotech products, the likely consequences of the changes in the manufacturing process, and also the issues of product quality, safety and efficacy. Although these regulations could be seen as an important step in the right direction there are still a number of uncertainties, including the issue of the documentation necessary for an approval[14]. The European Union and EMEA are pioneers in the formation of the regulatory pathways for biosimilars. It is interesting that the similar agency for drug evaluation in the US, i.e. the Food and Drug Administration (FDA) is still working on the final version of the guidelines on follow-on-biologics. In fact many patents for original biotech medicines will expire later in the US than in the EU (e.g. epoetin alfa) (Table I).

The most important issue of the current European guidelines is the notion that biotech medicines cannot simply be copied as has been the case with conventional chemical medicines. This recognition is crucial with respect to the safety of the new biotech products which are expected to enter the medical market. The Guidelines indicate that biosimilar manufacturers need to identify a single reference product and conduct tests to demonstrate biophysical similarity. The manufacturer must also provide sufficient non-clinical and clinical data to demonstrate clinical similarity to the reference product. An efficacy study with an appropriate indication is required if the reference product has multiple indications. Biosimilar manufacturers may extrapolate to other indications if the mechanism of action is the same and if appropriately justified. In case of the biosimilar recombinant human erythropoietin the new product will have to be tested in at least two efficacy studies in chronic kidney disease patients including one titration study in epoetin-naïve patients and one maintenance study in patients already treated with erythropoiesis stimulating agents[15,16]. The guidance also requires sufficient immunogenicity data to be provided before approval. This is a very sensitive issue in nephrology and the recent lesson from an unexpected rise in the number of cases of pure red cell aplasia (PRCA) in patients treated for renal anaemia with recombinant erythropoietin must be remembered[1].

It is quite clear that the EMEA Guidelines do not answer all questions that could be raised on biosimilar products, and the appropriate legislation should be introduced at the national level of EU member states. So far the leading country is France where the three societies of renal medicine professionals, i.e. French Society of Nephrology, French Society of Paediatric Nephrology and French-speaking Society of Dialysis issued a position statement on the use of biosimilars[17]. Shortly after that statement was issued in 2006, the French Parliament on 6 February 2007 adopted the first legislation covering biosimilar medicines in the European Union transposing the European Directive 2004/27/EC[18]. French law on biosimilars states clearly that biosimilars cannot be classified as "generics" in the same way as chemical medicines, and bans automatic substitution of one biological medicine over another. The French pioneer initiative is an important step forward and more national laws are expected to follow.

WHAT ARE THE MOST IMPORTANT ISSUES WITH BIOSIMILARS?

Safety

Since biosimilars are by definition only similar but not identical to the reference product each of the products has a unique safety profile[1]. The safety profile is dependent on the specific mechanism of action, unique cell-line used for the production, manufacturing process and its control, and composition of the final product (including by-products and impurities). The most important safety issue of biotech medicines is immunogenicity. It is quite clear that all therapeutic proteins have the potential to induce antibody responses. Such immunologic reaction may develop as an initial response to therapeutic protein and later a broad response (e.g. serum sickness). The latter includes endogenous proteins. In most cases, no clinical consequences are found but in rare cases antibody-related reaction can be serious and even life-threatening. The development of antibodies may lead to a neutralisation of a therapeutic protein including also an endogenous hormone. That was the case with recombinant erythropoietin[19,20]. The anti-

bodies may also cause either a loss or enhancement of efficacy. Unfortunately, immunogenicity of biosimilars cannot be predicted with preclinical or non-human studies and in some cases could only be detected after a long-time treatment with the biotech medicine. Therefore, not only are clinical immunogenicity studies required pre-approval but also robust pharmacovigilance is necessary for many years after the introduction of the treatment[19]. Pharmacovigilance is critical for the safety issue and requires the combined efforts of doctors, regulatory bodies and pharmaceutical industry.

The recent problem with PRCA among patients treated for renal anaemia with recombinant erythropoietin added much to our knowledge and awareness of the potential problems with biotech medicines. The outbreak of cases of PRCA was caused by the development of neutralising antibodies directed against recombinant erythropoietin[20] which led to severe epoetin-resistant anaemia that required blood transfusions and immunosuppressive treatment. Most disturbing is the fact that an outbreak of PRCA occurred more than 10 years after the introduction of recombinant human erythropoietin for the treatment of renal anaemia and the problem was most likely a consequence of only a small modification of the drug formulation[21]. According to the manufacturer, the factors that might have played a primary role in the cases of PRCA were a shift from intravenous to subcutaneous administration with an accompanying increase in patient self-administration and the replacement of the stabilizer, human serum albumin with polysorbate 80, which could have led to an interaction of the latter with the uncoated rubber stoppers used in prefilled syringes[22]. After the likely sources of the problem had been identified, changing the stoppers and switching the route of drug administration from subcutaneous to intravenous route caused PRCA to almost disappear in the following years (figure 1)[22].

It is very likely that we might not yet be aware of many potential side-effects of many biotech medicines, especially those that may only develop after a long-term treatment. This will require an appropriate pharmacovigilance. The issue of pharmacovigilance is not unique to biosimilars but has been without any doubt highlighted and heightened by their arrival[23]. The pharmacovigilance must ensure traceability of the products. Companies and regulatory

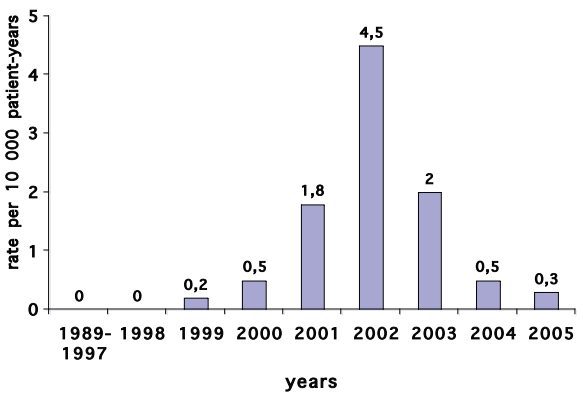

Figure 1

Reporting rates of erythropoietin antibody-positive PRCA per 10,000 patient-years among patients treated for renal anaemia (all forms and routes of administration) through 30 November 2005. Available from: http://www.jnjpharmarnd.com/company/n-casereports.html

agencies must distinguish one manufacturer's product from another. This is, however, very difficult when biosimilars have the same international non-proprietary name (INN) as the innovator and can be automatically substituted. Such practice is still allowed in most countries. It is obvious that uncontrolled substitution will confound accurate pharmacovigilance.

Automatic substitution, naming and labelling of biosimilars

The substitution of a prescribed drug could occur in two ways; the pharmacist overrides the prescription of the physician or chooses a product from the same INN class. In the first case, the physician prescribes a brand or a specific generic and the pharmacist overrides with an alternative "generic" without consulting the physician. In the second case the physician prescribes by INN but does not specify manufacturer and the pharmacist chooses one of the products with the same INN. In practice such choice is usually based on the price of the drug or personal experience. In both cases, however, substitution can occur without knowledge or consent of the physician[24].

In most countries of the European Union, medicines with the same structure of the molecule having the same INN name can be substituted. Most of us recognise such substitution as safe and this is often concordant with our own professional experience. It is therefore universally recognised that in the

case of generics (copies of chemical drugs) the risk of substitution is low except in drugs with a narrow therapeutic window (e.g. slow-release theophylline, anti-convulsants, anti-arrhythmics or cyclosporine A). In many countries the automatic substitution of those drugs is not allowed, and appropriate warnings can be found in their summary of product characteristics (SmPC).

In the case of biosimilars, it is quite clear that the same substitution rules as for conventional chemical drugs cannot be applied since biotech medicines are never identical[24,25]. Also, the safety profiles of a biosimilar and the reference biotech product are different. Therefore the existing (e.g. French) and future regulations should prevent inappropriate substitution for biosimilars[17,18,24,25]. If substitution happens with biosimilars it would decrease the safety of the therapy and prevent the traceability of drug side-effects. The future regulations on biosimilars should guarantee physicians that automatic/generic substitution rules should not apply and any decisions to substitute one biotechnology medicine with another should be made with the knowledge and explicit prior consent of the treating physician[24].

The WHO International Non-proprietary Name (INN) system has been introduced to identify every medicinal product. The system is important for the clear identification, safe prescription and dispensing of medicines to patients and for communication and exchange of information among doctors and scientists worldwide. The generic versions of chemical medicines are assigned the same name as they are identical copies of the reference product. The WHO is currently deciding whether biosimilars should be assigned a different INN to that of the original biotech medicine[24].

Since biotech medicines cannot be identical, labels of originator and biosimilar products must be different. Physicians, pharmacists and patients should be aware of the data available to support an introduction of a medicine to the therapy. Furthermore, unique safety data should be included (including the potential formation of antibodies) and substitution warning should be provided. In the case of a biosimilar, the SmPC should be transparent and clear, and reference product should be defined[25].

In summary, advances in biotechnology have revolutionised the treatment of many diseases and most areas of medicine, including nephrology. There are many new original biotech medicines in development. It is expected that biosimilars will also increasingly become available and they will provide alternative treatment options for many diseases. Physicians should be aware that quality, safety and efficacy issues in biotech medicines and biosimilars are much more complex than in traditional chemical drugs and their generics. Substitution rules between originator and biosimilar products must also be different since these products and their safety profiles are never identical. Awareness of the differences between original biotech medicines and biosimilars is essential for patient safety.

Conflict of interest. None declared.

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