Editorial

Biosimilars are not (bio)generics

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Biological drugs are well established in the treatment of many conditions, with the likelihood of increasing use in future years. These therapies include the products of biotechnology such as recombinant proteins and antibodies (collectively termed biopharmaceuticals) as well as several older drugs produced through purification techniques such as heparins and conjugated oestrogens. Biosimilars (Europe) or 'follow-on' biologics (USA) are biological products that are similar, but not identical, to an innovator product that is already marketed and whose patent has typically expired. Biosimilars cannot be considered 'generic' equivalents of innovator products as they are not necessarily clinically interchangeable and in some cases may exhibit different therapeutic effects. It is critical that physicians and pharmacists truly understand the complex factors which apply to this new and challenging area.

In this issue…

Many people travel during the Christmas holidays. Those travelling long distances by air will be interested in the review of flying and thromboembolism by Frank Firkin and Harshal Nandurkar.

International travel can contribute to the spread of infectious diseases including influenza. Several vaccines designed to control the spread of influenza are reviewed in the new drugs section.

Flying can cause earache, but ear infections are a more common problem in children. Peter Morris and Amanda Leach examine the evidence supporting the treatments used to manage otitis media.

Mouthwashes can be used to manage dental plaque, but Camile Farah, Lidija McIntosh and Michael McCullough say that these products have their limitations. They also warn that some mouthwashes have adverse effects, including a controversial association with oral cancer.

Controversy has also surrounded the use of mifepristone in Australia. Although the focus has been on abortion, David Healy informs us that the drug has several other potential uses.

Biological drugs are far more complex than conventional small molecule pharmaceutical products. Whereas conventional drugs can be completely characterised on the basis of their chemical structures, biological drugs tend to be recombinant three-dimensional proteins with structural complexity and a high molecular weight. This makes them difficult to characterise. The complexity of biological drugs also emanates from the elaborate manufacturing processes involved in their production.[1]

A major concern with biological drugs is immunogenicity.[1] As these products are often manufactured in living cells (for example hamster, rabbit or bacterial cells), they are considered foreign by the human body and induce immune responses such as neutralising antibodies. Immunogenicity can be affected by various factors including manufacturing processes and impurities. Impurities may derive from chemicals or antibiotics used during production or from microbial or viral contamination. These can compromise the purity of the final protein and may alter its structure or properties.

The imminent patent expiry of many biological drugs will open the door for greater numbers of biosimilars to enter the market. Marketing approval of biosimilars is a much more complicated issue than approval of generic equivalents of conventional drugs. The clinical performance of biological drugs is highly dependent on the method of production and purification. Immunogenicity can be altered with different formulations or different manufacturing processes (that is, differences in host cells, purification and processing, formulation and packaging). Verifying similarity or comparability of a biosimilar with an innovator product therefore requires much more than demonstrating bioequivalence, which is sufficient for conventional generic drugs. The need for vigilance related to the immunogenicity of biological agents was highlighted by the development of antibody-associated pure red cell aplasia in patients treated with recombinant erythropoietin (epoetin) following a relatively simple manufacturing change.[2]

Analytical tests can characterise molecular mass, protein content, glycosylation pattern, *in vitro* activity, physicochemical integrity, stability, impurities and additives of a biosimilar product. However, these analyses will not guarantee equivalent efficacy and safety to the innovator drug in the relevant patient population.

The therapeutic equivalence of biosimilars and innovator drugs can be assessed in a switching study where patients are switched between the two products. This determines whether the biosimilar induces an immunological response (using assays to detect neutralising antibodies), and whether efficacy and safety are affected when products are switched.[1] The results of such a trial determine if the sponsor of a biosimilar can claim for interchangeable use with the innovator product. These studies are costly and time-consuming. As the complexity of the protein product increases, such as with long-chain or heavily glycosylated proteins and monoclonal antibodies, more clinical data are required to fully characterise the clinical properties of the biosimilar.

The European Union has taken a global lead in establishing guidelines for the approval of biosimilars. As of January 2008, four biosimilars have been approved in Europe – two human growth hormone analogues and two erythropoiesis-stimulating agents. The Therapeutic Goods Administration has adopted the European Medicines Agency (EMEA) guidelines[3] on the non-clinical and clinical requirements for a biopharmaceutical. The guidelines call for far more rigorous testing than would be needed for a chemical generic product. These requirements include pharmaco-toxicological assessment, and pharmacokinetic, pharmacodynamic, efficacy and clinical safety studies.[4]

Due to the unpredictability of the onset and incidence of immunogenicity, postmarketing surveillance is a priority with biosimilars. The European guidelines require the manufacturer to submit a comprehensive pharmacovigilance plan with a focus on monitoring immunogenicity after the product has been marketed. This plan must be established at the time of marketing approval.[4] Also, stringent quality control guidelines recommend that both innovator and biosimilar manufacturers ensure consistency in their production by performing rigorous purity and activity profiling between batches.[5] Providing clinicians with the product summary, the evaluation of the clinical data used for approval, and advice about substitution will be critical for patient care.

Biopharmaceuticals are relatively expensive compared to chemical drugs because of their complex manufacture and clinical development and the costs of handling, distribution and delivery systems. The main reason for using a biosimilar is that it is cheaper than the original product.[6] However, the potential cost-savings associated with biosimilars will be less than the savings from ordinary generics. This is due to the higher manufacturing costs, more extensive testing requirements – generally efficacy and safety have to be demonstrated separately for each of the claimed indications[7] – and the need for a postmarketing pharmacovigilance plan.

Incorporating biopharmaceuticals as therapeutic options into patient management is the new reality. Awareness of the quality, safety and efficacy issues and the differences between biosimilars and innovator products is essential for patient safety. Any decisions to substitute one biopharmaceutical with another should be made with the knowledge and prior consent of the physician. In particular, pharmacovigilance is a shared responsibility between the pharmaceutical industry, physicians, pharmacists, nurses and patients.

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