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Biosimilar vs biological agents in rheumatology: When are biosimilar agents similar enough?

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ABSTRACT

With the introduction of biological agents, over the last two decades treatment prospects in many medical fields including Rheumatology have experienced an exciting revolution. The advent of biological therapy for specifically rheumatic diseases has provided more effective control of both the underlying disease, and sustained amelioration of disease activity, compared to the pre-biological era when only anti-inflammatory and immunosuppressant drugs were available. Although the importance of potential improved clinical outcome cannot be overstated, these efficacious treatments for rheumatic diseases are not without a high cost. Biological agents are expensive and rheumatological diseases are common. The patent and regulatory data protection periods for the first and second waves of biological agents based on recombinant proteins have begun to expire, leaving open the potential for development and regulatory approval of one or more "generic" versions of these biological therapies, termed "biosimilars" or "BSs" in Europe (the term we shall use from henceforth), "subsequent entry biologics" in Canada, or "follow-on-biologics" in US.
We aimed to review the critical topics of efficacy, safety and regulatory approach of upcoming biosimilars.

1. Introduction

With the introduction of biological agents, over the last two decades treatment prospects in many medical fields including Rheumatology have experienced an exciting revolution. For example these drugs have led to a completely new approach to the management of patients with inflammatory autoimmune conditions [1]. The advent of biological therapy for specifically rheumatic diseases has provided more effective control of both the underlying disease, and sustained amelioration of disease activity, compared to the pre-biological era when only anti-inflammatory and immunosuppressant drugs were available. Treatment to induce complete remission is now possible.

Although the importance of potential improved clinical outcome cannot be overstated, these efficacious treatments for rheumatic diseases are not without their cost. Biological agents are expensive and rheumatological diseases are common. As such even the wealthiest societies are unable to support the indiscriminate widespread use of biological agents in all patients requiring biologics [2,3].

However, the patent and regulatory data protection periods for the first and second waves of biological agents based on recombinant proteins have begun to expire, leaving open the potential for development and regulatory approval of one or more "generic" versions of these biological therapies, termed "biosimilars" or "BSs" in Europe (the term we shall use from henceforth), "subsequent entry biologics" in Canada, or "follow-on-biologics" in US. The development of biosimilar therapies could lead to a substantial saving for patients and health systems, and therefore increased availability of effective treatment to a wider patient demographic [4].

BSs are similar, but crucially not identical to their reference products, because their chemical characteristics are directly related to the manufacturing process which cannot be faithfully replicated [5]. Thus, despite the hypothetical promise of cheaper drugs compared to the reference biologic that also don't compromise on efficacy, these agents have provoked major concerns concerning their short and long term safety-something that must be addressed by regulatory agencies before BSs may be approved. Biosimilars of etanercept and rituximab have already been approved in countries such as India, China and South Korea [5]; their possible emergence in European and US markets is currently a matter of discussion by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) respectively [4].

1.1. Definition of biosimilars (BSs)

Biosimilars are defined as "biological products similar, but not identical, to their already authorized biological reference drug", whereas generic drugs are "precise copies of drugs with the exact same pharmacological effects, side effects, risks, safety profile and

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strength as the reference drug". Thus, BSs are not generic versions of biological products.

1.2. Regulatory approval

Limited documentation is required to obtain this marketing authorization for a conventional small-molecule generic drug. In general, to obtain market authorization it is necessary to show pharmaceutical equivalence (i.e. identical active substances) and bioequivalence (i.e. comparable pharmacokinetics) between the generic and its reference drug. This can often be done in a small study of volunteers, via an abbreviated procedure, and formal clinical efficacy and safety studies are not necessary.

However, this approach cannot be extrapolated to BSs and Biologics. Unlike conventional small-molecule drugs and their generics, the active substance of a biological agent is a collection of large protein isoforms and not a single molecular entity. Generating an exact replica of a protein molecule is extremely difficult if not impossible. Hence it is highly unlikely that the active substances will be identical between the two products — that is pharmaceutical equivalence is difficult to demonstrate. Moreover there are currently no analytical techniques to establish bioequivalence between a BS and reference biologic. Physicochemical and biological methods for characterization of biological agents such as monoclonal antibodies (mAb) are becoming increasingly sophisticated, but the ability to compare a biosimilar mAb to a reference mAb on an analytical level remains limited. Therefore compared to generic drugs, to illustrate the pharmacological profile of a BS necessitates a more rigorous process, and the amount of data required for market approval of BSs will be considerably more than for a typical generic drug application.

Table 1 shows general agreed standard definitions for conventional generic agents, biological agents and BS based on terminology used by the EMA.

At present the EMA guidelines are the only clear document detailing the requirements for market approval of biosimilars. The EMA guidelines advocate pre-clinical and clinical testing of BSs to demonstrate safety and efficacy prior to market authorization, followed by tailored pharmacovigilance plans to monitor potential immunogenicity.

Moreover, the European guideline states that if the reference medicinal product has more than one indication, the efficacy and safety of a BS has to be justified, or if necessary, demonstrated separately for each of the claimed indications. However, the guideline also introduces the caveat of 'extrapolation' of data regarding efficacy and safety from trials designed for other indications for which a BS has not been tested. This would be only in specific circumstances, where the mechanism of action is the same, as was seen in the case for the hematopoetic hormones erythropoietin and granulocyte-colony stimulating factor.

In the United States, the FDA has not yet issued a specific regulatory pathway. The Biologics Price Competition and Innovation Act (BCPI) outlined a shortened approval process for "highly similar" biological products, which enables a biosimilar product to be evaluated against a single, already licensed, reference biologic therapy. In February 2012, the FDA issued a draft guidance for the industry regarding implementation of the BPCI Act approval process for BS agents [6–10]. Data obtained from analytical and animal studies, and from at least one clinical trial conducted in patients with a disease for which the biological agent is licensed, will be required to demonstrate that a BS product is highly similar to the reference product [2,10].

However, the draft guidance does not specify requirements for the size or duration of the required clinical trial, and the FDA has not yet indicated whether the trials will be required to demonstrate non-inferiority, or prove therapeutic equivalence, of the BS agent — therefore leaving a margin of uncertainty.

The position of the American College of Rheumatology (ACR) has been also reported, stating that to enshrine the safety of patients, decisions concerning biosimilarity and interchangeability must be driven by scientifically-sound evidence. The ACR strongly believe that safe and effective treatments should be available to patients at the lowest possible cost [11].

Although there are no definitive rigid sets of guidelines regarding BS regulatory body approval, general unifying principles include prioritizing high similarity to the reference product, clinical trials demonstrating efficacy and safety, and a commitment to further safety profile follow-up after the drug has been approved on the market [10].

Table 1
General agreed standard definitions for conventional generic agents, biologic agents and biosimilars, based on terminology used by the European Medicines Agency (EMA).

Generic drug	A chemical and therapeutic equivalent of a low-molecular-weight drug whose patent has expired
Biological agents	A medicinal product developed by means of one or more of the following biotechnology practices: rDNA, controlled gene expression, antibody methods
Biosimilar	A biological medicinal product referring to an existing product, submitted to regulatory authorities for marketing authorization by an independent application, after the time of the protection of the data has expired for the original existing product

1.3. BSs and rheumatic disease: clinical efficacy and safety

In a poll of US, French and German physicians in 2010, it was unanimous that efficacy compared to reference biologic was the most important deciding factor when considering whether to prescribe BS [12]. Although efficacy of a BS should be theorically equivalent to its reference product, numerous contributing factors may mean that this is not the case. Product attributes related to manufacturing approach (including in-process controls and product controls, impurities, aggregates, heterogeneity, fragments) differ between a BS and biologic. Thus, even in cases where a well-established potency assay correlating with clinical efficacy is available, to convincingly exhibit clinically equivalence, human data would likely be required for BS development [5].

Data from physicochemical and biological characterization alone are not sufficient for BS development, and data coming from clinical trials are required to support similarity. The key question is, to what extent clinical trials are required for a BS? The goal of the clinical development program for the BS is to demonstrate no significant difference compared to the reference product. For that, equivalence trials of adequate sample size that are ideally double-blinded should be conducted.

In August 2012 results from only one published trial was identified by searches including MEDLINE, Current Contents, PubMed, and amplified using a web-available search engine. Gu et al. reported a randomized, open-label, single-dose, two-sequence, crossover study in healthy Korean male volunteers compared with pharmacokinetics and tolerability of branded etanercept (25 mg) and its BS (25 mg) [13]. Twenty-five healthy Korean men were enrolled in this study and randomized to receive either the BS or the reference drug. In terms of safety, they reported that 52.4% of the patients receiving the BS and 38.1% receiving the reference drug experienced some adverse events, mainly headache, throat irritation, and epistaxis. The authors also described that the tested BS agent had a pharmacokinetic profile consistent with profiles previously reported in other etanercept pharmacokinetic studies. They concluded that, in a select group of Korean healthy male volunteers, branded etanercept and its BS were well tolerated and met the standard criteria for assuming bioequivalence as defined by Korean regulatory authorities. This data would of course need further confirmation and substantiation in other larger and double-blinded trials.

1.4. Safety

As biologicals, BSs are structurally complex proteins with significant micro-heterogeneity, produced by genetically modified living cells, and difficult to produce and purify. Manufacturing processes in terms of choice of cell type, production, purification, and formulation methods, all influence the quality, purity, biological parameters, and eventual

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