Clin Rheumatol (2012) 31:1289–1292
DOI 10.1007/s10067-012-2066-5

REVIEW ARTICLE

Subsequent entry biologics/biosimilars: a viewpoint from Canada

Anthony S. Russell · Vandana Ahluwalla · Cheryl Barnabe · Shahin Jamal · Robert C. Offer · Wojciech P. Olszynski · Kam Shojania · Boulos Haraoui

Received: 1 August 2012 / Accepted: 9 August 2012 / Published online: 26 August 2012

Abstract We have reviewed the issues surrounding the advent of biosimilars in the rheumatoid arthritis biologic field. Our proposals emphasize the need to focus primarily on patient safety and to assess the outcomes of therapy both in the short and longer term.

Keywords Biosimilars · Subsequent entry biologics

Biologics, which for the purposes of this paper refer to the drugs as they are used in rheumatology, are very complex molecules. They are made with the aid of DNA recombination technology and are secreted by cells, bacteria, or plants, which have incorporated the appropriate genes. The drugs are then harvested from the secretions. Sometimes a "second-generation" biologic is made that is structurally different from the original molecule and these are intended to improve performance or perhaps decrease immunogenicity while preserving the mechanism of action. The development of golimumab subsequent to infliximab might be considered an example of this. These second-generation products are not usually considered to be "follow-on" products. Such follow-on products, which are also known as biosimilars or in Canada, subsequent entry biologics, are intended to be sufficiently similar to the reference product that there is no clinically meaningful difference between them in terms of safety, purity, and efficacy. Therapeutic substitution is the interchange of a less costly drug in place of another treatment, based on the premise that the cheaper version has the same therapeutic effect. The generic forms of a reference drug are usually marketed after the patent of a branded agent has expired. A generic drug contains an active component, normally a small molecule, which is qualitatively and quantitatively identical to the reference drug, although the excipients may differ. Marketing the generic form requires only an abridged procedure as it is not a new chemical in its entity. A demonstration of bioequivalence is required and this is normally done in healthy volunteers to compare the bioavailability between the test product and the reference product. For all agents, this will include a comparison of

A. S. Russell (✉)
562 Heritage Medical Centre, University of Alberta,
Edmonton, AB T6G2S2, Canada
e-mail: as.russell@ualberta.ca

V. Ahluwalla
227-40 Finchgate Blvd,
Brampton, ON L6T3J1, Canada

C. Barnabe
University of Calgary,
3330 Hospital Dr. NW,
Calgary, AB, Canada

S. Jamal
Vancouver Coastal Health Gordon and Leslie Diamond Centre,
2775 Laurel St. Suite 8205B,
Vancouver, BC V5Z1M9, Canada

R. C. Offer
112-725 Carmi Ave,
Penticton, BC V2A3G8, Canada

W. P. Olszynski
Centre 103 Midtown Medical Centre,
39 23rd st. E,
Saskatoon, SK S7K0H6, Canada

K. Shojania
Division of Rheumatology, University of British Columbia,
#802-1200 Burrard St.,
Vancouver, BC V6Z2C7, Canada

B. Haraoui
University of Montreal,
1551 Ontario Est,
Montreal, QC H2L1S6, Canada

absorption, rates of absorption, and peak concentrations. Equivalence is inferred when for both AUC and Cmax, a 90 % confidence interval for the ratio of geometric means for test and reference formulation lies within the range of 0.8 to 1.25. However, even with these boundaries, there is some concern regarding using generics, specifically, for example, in the area of bisphosphonates [1]. At the 2011 ACR meeting, it was suggested that a biosimilar does not need to be identical to the original biologic, but what must be an exact copy is the protein's amino acid sequence. What is expected is that the biosimilar products will produce the same clinical result in any given patient as the reference drug.

The question that is critical to address is when is a copy good enough to be treated as the real thing? In the recent discussion at the ACR in 2011, it was pointed out that patents of several top-selling biologic agents in rheumatology are expected to expire in the next few years, making this question increasingly important. A large biologic such as a monoclonal antibody measures about 150,000 Da has more than a 1,000 amino acids and degrades over time, usually requiring special storage to maintain stability. Glycosylation and other post-translational modifications may also be critical for function. On the other hand, a small molecule drug such as omeprazole is 345 Da and is stable and has a much lower potential for immunogenicity than do monoclonal antibodies.

Clinical trials of subsequent entry biologics (SEBs)/biosimilars are ongoing in Canada at this time and some of the concerns raised include the following:

1. Will the drug be as effective as the reference drug?
2. Will it be as safe as the reference drug, both in the short and long term?
3. Will it be as well tolerated as the reference drug? Will the rates of infusion and/or injection site reactions be similar?
4. If a biosimilar is substituted for a prescribed drug, will this have any adverse impact?
5. How will the pricing of RA biosimilar products affect the over-all price of the RA biologic class?
6. Where will the therapy be administered and will they require similar co-medications as the reference drug?

Manufacturing It is as important for SEBs/biosimilars as for the reference drug that there be development of a manufacturing process that consistently produces drug substance within the accepted normal batch to batch variation of the product as regard to the structural features that are most important for the SEB/biosimilar's function. Biosimilar products are required to be "highly similar to the reference product, notwithstanding minor differences in clinically inactive components" and exhibit "no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity and potency of the product" (BPCIA 2009) [reviewed in 2–6]. The European Medicines Agency (EMA) guidelines are similar [6, 7]. What such clinically meaningful differences amount to in quantitative terms requires definition. Ideally, the SEB would show differences no greater than that between different batches of the reference drug but that latter information is often unavailable. Another approach would be to frame it in terms of the outcomes measured, e.g., the ACR20-70, DAS, SDAI, etc. responses should be within 10 % of that found with the reference drug. It would be expected that the SEB should show similarity for all of the claims established for the reference drug, e.g., QoL, structural damage inhibition, etc. Whether studies should be powered to show non-inferiority or equivalence remains undecided [3, 4]. Interchangeability requires a higher standard that the product "produces the same clinical result as the reference product in any given patient" and "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product (biosimilar) and the reference product is not greater than the risk of using the reference product without such alterations" [2]. This latter issue is unlikely to be tested in controlled clinical trials.

Manufacturing changes are not rare even by the original developers of biologics and this can sometimes have a beneficial effect. For example: interferon beta 1A, originally made by Biogen Idec in a Chinese hamster ovary cell line, was made in a new cell line and named Avonex. It had decreased immunogenicity when compared to the original agent [6, 7]. Currently, an important change in the manufacturing process even by the original manufacturer requires approval. This has been seen with the development of subcutaneous abatacept, after approval of the intravenous preparation. Prior to its approval, safety efficacy and pharmacokinetic studies were required in adequate numbers of patients.

Data would normally be obtained from analytical and animal studies and then from at least one clinical trial conducted in patients with the disease for which the reference product is licensed. This could allow the demonstration that such a biologic product is "highly similar to the reference product."

Biosimilar products are currently being manufactured in China, for example, and used in that country and companies are certainly starting in this field in Israel, Taiwan, and Korea, to name a few. In some cases, there seems to be little in the way of data regarding its efficacy. An example of this is Reditux, a biosimilar form of rituximab manufactured in India by Dr. Reddy's Laboratories, which is used in Peru and India.

Extended indications This question remains controversial, i.e., whether if a SEB has shown equivalence to a reference drug in patients with rheumatoid arthritis, the equivalence still needs to be shown for other diseases for which the reference drug is approved. The issue does need to be addressed in initial regulations, and in the early stages presumably it cannot be routine, and will require data; although once the area is more advanced, such extended indications could become routine.

Immunogenicity A considerable problem for establishing an abbreviated regulatory pathway is the potential immunogenicity of the drug. For endogenous proteins, concerns of immunogenicity are heightened. One example of this is erythropoietin where immunogenicity has had significant consequences with the development of pure red cell aplasia in a small number of patients; however, it may have been a change in the formulation of recombinant human erythropoietin, i.e., a change in the protein stabilizer from albumin to polysorbate that led to the development of antibodies, which cross-reacted with endogenous erythropoietin [8]. Thus, there is now a formal EMA requirement for an extended pharmaco-vigilance plan that must be approved and in place. However, for nonendogenous proteins, concern will generally focus on immunogenicity-related adverse events and on immunogenicity that alters in a meaningful way the pharmacodynamics or pharmacokinetics of the SEB/biosimilar or its long-term durability. The corollary to this is that biosimilars should have their own specific name such as "infliximab-celltrion" rather than simply "infliximab."

As a specific example, rituximab by Pfizer is a geneticall-y engineered chimeric mouse–human IgG 1 monoclonal antibody directed against a CD-20 antigen. It comprises 213 amino acids, which is the same primary amino acid sequence as the reference product, rituximab produced by Roche. High-resolution analytical methodologies were used to assess posttranslational modifications, like terminal amino acid sequence, oligosaccharide analysis, charge aggregation, and higher order structure .Similarly, in infliximab produced by Celltrion, even though the culture cells, etc. are the same, it had to be carefully monitored and modified to mimic the identical glycosylation structure.

Regulatory framework The regulatory framework for SEBs varies in different countries [2–6]. Many have established SEB/biosimilar pathways or at least draft guidelines. The first was provided by EMA in 2005 and provided a framework for others to build on. Some drugs have been rejected [6]. WHO issued guidance in 2009. The assessment of similarity with the reference drug is to be performed throughout the development of the product and will include physicochemical properties, biological activity, immunochemical properties, process- and product-related impurities, and stability. The preclinical studies should be conducted with the final formulation of the SEB intended for clinical use. Demonstration of pharmacokinetic similarity between the SEB and the reference drug is an essential component of this program [9]. Equally, pharmacodynamic assessments are chosen based on their ability to predict clinical outcomes. Ultimately similar efficacy of the SEB/biosimilar reference drug will generally need to be demonstrated in adequate randomized and controlled trials. Clearly, however, no placebo component will be required in those studies.

Health Canada has developed guidance and clarifications on SEBs which could have broader implications [8]. According to Health Canada [10]:

- Biosimilars are not "generic biologics."
- Marketing approval for a biosimilar is "not a declaration of pharmaceutical or therapeutic equivalence to the innovator drug."
- Each approved biosimilar "is considered to be a new ('stand-alone') product with all of the associated regulatory requirements."
- "Comparative clinical trials are critically important to demonstrate the similarity in efficacy and safety profiles" between the biosimilar and the innovator drug. This means that they have to be tested in humans, and that the testing has to be robust enough to detect differences.
- For generic drugs, pharmacists are often required to ensure that the cheapest version of the chemical drug is dispensed, even if the physician writes a prescription for the brand version of a drug. This is called interchangeability. Drugs may also be considered substitutable, which allows physicians to substitute one version for another (usually cheaper) version. For biologics, Health Canada does not support interchangeability and substitutability (as it does for most generic, small molecule drugs) and recommends for prescribing decisions that "physicians make well-informed decisions regarding therapeutic interchange." [ii]
- To date, only one drug, the recombinant human growth hormone Omnitrope, has been approved by Health Canada as a SEB. Most provincial healthcare systems and healthcare professionals are treating Omnitrope as one new option in an established class of therapies.
- In Canada, few provinces have yet to announce how SEBs will be reviewed and reimbursed. British Columbia (BC) PharmaCare has cited that SEBs are required to complete a review via the Common Drug Review prior to a review by BC PharmaCare. However, BC PharmaCare has not indicated how robust the clinical trial program of an SEB will be required nor whether these products would be

preferentially reimbursed over other RA biologics. Alberta is the only province that specifically excludes SEBs from being considered as interchangeable.

Summary

In order to achieve optimal, patient-centered outcomes:

1. SEBs must have an acceptable safety and efficacy profile: Significant clinical trial data using accepted outcomes should be required to demonstrate a satisfactory safety profile for each SEB product. At this point, a SEB manufacturer should be required to provide the same information on their product's safety and efficacy as the brand name product to which it claims similarity for each specific diagnostic indication. There should already be a national approved brand name biologic to which the SEB in question can be compared for similarity.
2. SEBs are not interchangeable with each other nor with brand name biologics: Given the complexity of manufacturing processes of biologic products and the safety concerns highlighted by SEB non-approvals and rejections by the EU, SEB products cannot be declared "interchangeable" with brand name biologics. While Health Canada has clearly stated that SEBs are to be considered "similar" to their brand name biologic, provincial drug plans have yet to formulate the same policy.

Doctors and patients should remain free to select the most appropriate biological therapy based on the patients' needs and its history of safe use and clinical response. Decisions to substitute one similar product with another should only be made at a physician's discretion.

3. Each biologic product must have a unique product name: Each SEB product must have unique and distinguishable names and a distinct name under the International Nonproprietary Names Program of the World Health Organization. Given the fact that SEB products are not identical to innovator products and could have significantly different clinical outcomes for patients, physicians, pharmacists, and nurses must be able to readily distinguish SEBs on the basis of their names. A unique name will assist in the accurate prescribing and dispensing of SEBs and supports governments efforts to closely monitor adverse events. Without distinct names, patients, physicians, and pharmacists could become confused, leading to inadvertent product substitution. Consequently, if there are fluctuations in patients' responses, it could become more difficult to determine the source and therefore complicate the tracking of adverse events.
4. Cost must not override safety and efficacy: The cost of producing SEBs is clearly less than that of the brand name biologic to which it is similar. Assuring patient choice may be problematic for patients who rely on publicly funded biologics because prescribing physicians may be encouraged or compelled to prescribe the less expensive SEB, thereby potentially compromising patient outcomes, choice, and safety. Preferential listing of SEBs on provincial formularies should be discouraged if it is at the expense of patient safety, proven product efficacy, and physician–patient choice.
5. Strict post-market surveillance must be followed: Monitoring of SEBs must conform to the same rigorous standards as those used for brand name biologics. The traceability of SEBs must be assured through unique names. A registry, similar to, or integrated with those currently in use will be required to provide longer term monitoring of each specific, named, drug. Whether the required funding will be provided by the industry or other sources may vary.

Disclosures None.

References

1. Kanis JA, Reginster J-Y, Kaufman J-M et al (2012) A reappraisal of generic bisphonates in osteoporosis. Osteoporos Int 23:213–221
2. Colbert RA, Cronstein BN (2011) Biosimilars: the debate continues. Arthritis Rheum 63:2848–2850
3. Mullard A (2010) Hearing shines spotlight on biosimilar controversies. Nature Rev(Drug Discovery) 9:905–906
4. Sekhon BS, Saluja V (2011) Biosimilars: an overview. Biosimilars 1:1–11
5. Kogan LA (2011) The US biologics price competition and Innovation Act of 2009 triggers public debate, regulatory/policy risks and international trade concerns. Global Trade Customs J 6:1–34
6. Joshi SR (2011) Biosimilar peptides: need for pharmacovigilance. J Assoc Physicians India 59 suppl:44–47
7. Rudick RA, Simonian NA, Alam JA et al (1998) Incidence and significance of neutralizing antibodies to interferon-beta1a in multiple sclerosis. Neurology 50:1266–1272
8. Jelkmann W (2010) Biosimilar erythropoietins and other follow-on biologics: update on the European experience. Am J Haematol 85:771–780
9. Gu N, Yi S, Kim T-E, Shin S-G, Jang I-J, Yu K-S (2011) Comparative pharmacokinetics and tolerability of branded etanercept (25 mg) and its biosimilar (25 mg): a randomized, open-label, single-dose, two-sequence cross-over study in healthy Korean male volunteers. Clin Therapeutics 33:2029–2037
10. http://www.biosimilars.ca/docs/BIOTECanada-SEB-GOWLINGS-082310.pdf