

Biomedical and Market Issues Surrounding the Advent of Biosimilars

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Received: May 21, 2016 / Published online: June 21, 2016
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ABSTRACT

As the patents associated with the biologics are set to expire in the near future, a new type of therapy appears on the horizon, and it is quite similar to the biologics. This commentary examines the biomedical and market issues surrounding the advent of biosimilars.

Keywords: Biosimilars; Biologics; Inflectra; Infliximab; Interchangeable; Psoriasis; Remsima

COMMENTARY

The arsenal of treatments for psoriasis continues to grow. Originally limited to topical steroids, phototherapy, and systemic therapies, biologics

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have not only revolutionized treatment, but also provided more efficacious management. As the patents associated with the biologics are set to expire in the near future, a new type of therapy appears on the horizon, and it is quite similar to the biologics. Herein, we discuss the biomedical and market issues surrounding biosimilars; this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Created under the Biologics Price Competition and Innovation Act of 2009, biosimilars are less costly imitations that show high similarity to an already FDA-approved biological product, known as the reference product. In order to be approved by the FDA, a biosimilar product must show no clinically meaningful difference from the reference product. The biosimilar must have the same mechanism of action, route of administration, dosage form, and strength as the reference production [1]. In addition, a biosimilar can only be approved for the same indications and conditions that have been previously approved for the reference product. To be considered an interchangeable biological product, the

biosimilar must produce the same clinical result as the reference product in any given patient [2]. Once a biosimilar has been FDA approved, health care providers and patients will rely upon the safety and effectiveness of the biosimilar just as they would for the reference product.

Biosimilars have the potential to reduce treatment costs compared with those of reference products. While biologic agents may be more effective compared to most traditional systemic therapeutic options, their use is associated with a much higher cost. With annual costs ranging between \$13,000 and \$30,000 per patient, cost effectiveness is an important consideration for both the patient and the physician when choosing to use a biologic agent [3]. Biosimilars may hold the promise of being a cheaper substitution for biologics in the future, but their short-term cost rivals that of developing biologics.

To enter the market, biosimilars need to overcome barriers that are much more difficult than typically seen with small-molecule generic drugs. Safety, pricing, manufacturing, physician acceptance, and marketing differentiate the biosimilar market from the generics market. Compared to an average of 3 years and \$1–4 million between development and approval of a drug in the generic market, it takes 7–8 years to develop a biosimilar at a cost of between \$100 million and \$250 million [4, 5]. Also, companies may be reluctant to develop biosimilars because it may be just as hard to get the biosimilar approved by the FDA as it was for its reference biologic. To offset the cost and share the intrinsic risk of biosimilar development, pharmaceutical alliances between large, well-established companies are expected to dominate the market. Companies experienced in manufacturing, especially manufacturing biologics, will have a considerable advantage over new companies

with no such manufacturing experience [4]. For example, well-established companies such as Amgen and Hospira will likely lead because they already have the research, development, and marketing expertise required to produce biologics, while newer companies face a steep learning curve, a complicated manufacturing process, and a risky market.

Additionally, biosimilars consist of relatively large, complex proteins that are often more difficult to replicate, unlike generic medicines, which are chemical, small-molecule drugs that are equivalent in structure and therapy to the reference agent [6]. Contrary to chemical synthesis, the living systems in which biosimilars are produced are inherently variable. Biologics are manufactured through complex engineering that involves genetically modified unique cell lines designed to produce the desired antibody and purification processes that monitor for possible variations. Biosimilars are produced using different cell lines and extraction/purification processes than the reference product [7]. This results in heterogeneity due to variations in posttranslational modifications, such as glycosylation, or physical and chemical degradation, including deamidation, cleavage, and aggregation [6]. Therefore, biosimilars are not identical to the reference product and consist of a mixture of variants of the same protein. For this reason, evaluation includes pharmaco-toxicological, pharmacokinetic, pharmacodynamic, efficacy, and clinical safety studies with emphasis on the immunogenicity of the biosimilar.

Currently in Europe, two infliximab biosimilars have reached the market: Remsima and Inflectra. They are the same molecule (CT-p13), which is commercialized under two different names by the manufacturers Celltrion and Hospira,

respectively. Both are biosimilars to infliximab, the 1gG1 chimeric human-murine monoclonal antibody that targets TNF- α . The European Medicines Agency (EMA) approved these biosimilars after reviewing their efficacy and safety in a phase 1 pharmacokinetic study of patients with ankylosing spondylitis and in a phase 3 study evaluating efficacy in patients with rheumatoid arthritis [8, 9]. The EMA extrapolated from these studies to approve Remsima and Inflectra for treatment of psoriasis. More recently, four patients with severe psoriasis resistant to systemic therapies underwent treatment with Remsima [10]. Patients were treated with Remsima in a similar manner as with infliximab: 5 mg/kg IV at weeks 0, 2, and 6, and then every 8 weeks. After treatment, three of four (3/4) patients achieved almost complete remission, while the last achieved a reduction in skin symptoms. The study concluded that Remsima was comparable to infliximab in efficacy and safety, although the power to detect meaningful differences was limited [10].

Recently, the FDA approved the infliximab biosimilar Inflectra. Inflectra has been approved for the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. While Inflectra has been approved as a biologic, it is yet to be determined if it will be approved to be "interchangeable." A biologic approved as interchangeable may be substituted for the reference product without the prescriber's knowledge, and in the US, this can result in automatic substitution [11]. As such, determination of interchangeability requires a higher level of evidence. The biosimilar is expected to produce the same clinical result as the reference product in any given patient, and, if the biosimilar is administered more than once

to an individual, the risk of adverse events or diminished efficacy of alternating or switching between the use of the biosimilar and the reference product is not greater than the risk of using the reference product alone [1, 2]. However, the FDA has not yet established criteria that must be met to obtain the status of interchangeable, and it is unlikely that any biosimilar will receive that designation anytime soon [1]. Even if a medication were to be considered "interchangeable," legislation for automatic substitution is up to each state, regardless of the FDA's designation [12].

The interest in biosimilars is growing. The potential for automatic substitutions, the inherent variability that exists with biosimilars, and the possibility for immunogenicity and antibody formation are concerns that many dermatologists will have as biosimilars hit the market. While many hope that the introduction of biosimilars will improve access to treatment and lessen the economic burden on healthcare, it remains important that biosimilars undergo head-to-head comparison with the reference product at every step during development to ensure high similarity, safety, and efficacy. A biosimilar version of etanercept and adalimumab could be available in the US within the next 3 years. Already, clinical trials are underway to compare the efficacy and safety of etanercept and adalimumab to their biosimilar counterparts [13, 14]. Given the potential for differences in immunogenicity between the reference product and biosimilar, the postmarketing surveillance applied to biologics should also be applied to biosimilars. Postmarketing programs will determine efficacy and safety of biosimilars, while ensuring their similarity to the reference product.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this commentary or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Abigail Cline, PhD, and Jake E. Turrentine, MD, have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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