BioDrugs
https://doi.org/10.1007/s40259-019-00360-7

CURRENT OPINION

Biosimilars: A Value Proposition

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Abstract
Biosimilars are biological agents that effectively replicate original reference products. The main driver of their development is the promise of bringing competition into the marketplace, and consequently contributing to the sustainability of healthcare systems. By reducing financial barriers to biological therapies, biosimilars play a part in budgetary redistribution and, hence, in increasing patients' access to treatment. They also foster innovation and deliver other non-price-driven advantages. However, the market is such that harmonization of pricing of reference biologics and biosimilars may dissuade physicians from prescribing biosimilars and often creates an unfavorable market environment for the launch of biosimilars. Such dynamics result in a high cost by denying patients the full benefits and added value inherent in biosimilar agents. A more equitable offering of established original biologics and biosimilars is needed to ensure the viability of current healthcare services.

Key Points

Entry of biosimilars to the marketplace promotes the economic sustainability of healthcare and improves patient access to biological therapies.

Biosimilars confer more than economic benefits, exerting positive effects on biopharmaceutical innovation.

Healthcare policies that incentivize healthy competition may help solidify clinical acceptance and curtail market-driven manufacturer disinvestment, aiding patients overall.

1 Introduction

Given a choice between two products of equal quality that are indistinguishable in structure, function, and use, it seems reasonable to select the one of best value. However, value may have various connotations, which in terms of healthcare should be patient oriented. Such is the case for similar biological agents (i.e., biosimilars) and their reference counterparts. Both are quality products that are fundamentally alike in pharmacological properties, and administered under identical conditions for the same indications [1]. Although such an assertion is driven by science, there is also ample empirical support. An abundance (> 12 years) of clinical experience with biosimilars in Europe serves as validation, reflecting stringent guidelines for biosimilar development from the European Medicines Agency (EMA) [2]. Indeed, the EMA regulatory framework and its scientific principles have been acknowledged by highly regarded agencies and institutes, such as the US Food & Drug Administration (FDA) [3] and the World Health Organization (WHO) [4]. Because registered biosimilars and reference biologics are deemed essentially equal, why would prescribing one or the other be preferable? A fairly accurate (if not immediate and resounding) response to this question perhaps lies in practical experience acquired via biosimilar launches in Europe, past undertakings on generics, and the workings of pharmaceutical markets.

2 Biosimilars: Fostering Patient Access to Quality Biologics

Biosimilars are typically launched at discounted prices relative to reference biologics, generally triggering a decline in the cost of biological treatments overall [5]. This discount pricing frees up resources without reducing quality

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Published online: 07 June 2019

of care, to confer a net positive effect on healthcare sustainability. For instance, the microeconomic data published by *La Princesa*, a public hospital in Madrid (Spain), indicate that in the 2 years following the acquisition of an infliximab-bearing biosimilar medicine, treatment costs for a patient with Crohn's disease were reduced by 61% [6]. From a macroeconomic perspective, projected savings of 15 billion euro were anticipated across Europe between 2015 and 2020 [5].

The most notable impact of such cost effectiveness is the potential for healthcare budgetary redistribution, allowing increased patient access to biological therapies [7]. Patients in Eastern European countries, as well as those in countries with more entrenched healthcare systems such as Norway, Denmark, the United Kingdom, France, Germany, Sweden, and Spain, have benefitted in this regard [5, 8–10]. Furthermore, the reallocated funds may be used to improve healthcare services, acquire technologic upgrades or innovative medicines, or initiate biological therapy at earlier stages of a given disease [11]. The latter may likely apply to patients with lesser disease severities, conceivably altering long-term treatment paradigms. The creation of patient registries to amass more data through greater access will help gauge the enduring effects of biosimilars on disease progression.

3 Biosimilars: Value Beyond Price

There are other aspects of biosimilars that transcend monetary considerations. The extensive structural and functional analysis of reference products (in multiple batches) required by manufacturers of biosimilars have increased our understanding of molecular and functional properties of original biologics. For instance, in the course of a biosimilar candidate development, the functional importance of disulfide bonds in etanercept's biological activity has recently been discovered [12]. Furthermore, availability of two or more medicinal versions as a result of biosimilar commercialization mitigates the risk of shortages, a major concern of healthcare authorities [13, 14]. Moreover, patients otherwise denied biological therapy may ultimately qualify for recruitment in biosimilar clinical trials [15].

A seeming paradox to marketplace entry of biosimilars, namely the fueling of biopharmaceutical innovation, warrants separate discussion. Aside from the re-investing of revenues generated in new molecules, there are at least four other avenues by which biosimilars are linked to innovation. In response to perceived commercial threats posed by biosimilars, the originators of reference biologics may pursue new molecules or improve existing ones. Subcutaneous formulations of rituximab and trastuzumab were likely prompted by the threat of approval of the intravenous biosimilar formulations [16]. Such scenarios have been debated extensively in the purview of generics and are restricted by the need for a proper balance between competition and patent law [17, 18]. The manufacturing process of a biosimilar is also a source of innovation. Compared with reference products, higher batch-to-batch consistency is afforded by new bioproductive methods also involving novel in-process control analytic techniques [12]. Such state-of-the-art production technology may be reassuring for long-term treatment recipients. There are also legal provisions for innovation within the biosimilars themselves. Manufacturers may aim for higher stability, less immunogenicity [1], or easier and more efficient modes of delivery, as with follitropin alpha-bearing biosimilar products [19, 20]. Finally, once marketed, biosimilars have their own commercial lifecycle and may spawn novel evolutionary products. The current development of a subcutaneous formulation of infliximab, which is derived from an intravenous biosimilar medicine, is one such example [21]. Pharmaceutical innovation is a necessity and is clearly fostered by biosimilars.

4 Biosimilars: the Risk of the Cost of Opportunity

A key aspect of biosimilars is heightened marketplace competition. As a result, commercial rivals often lower costs of reference products to biosimilar levels; and in the absence of economic leverage, prescription of reference biologics tend to prevail. Market shares of reference products may even be extended through deep discounts. Such actions are major barriers to the commercial penetration of biosimilars and may spur divestitures in certain markets [22]. The European Commission legally enforces healthy competition, prohibiting some anticompetitive practices to ensure affordable medicines and preserve incentives for biosimilar launch [23]. Rebound price hikes are inevitable once a monopoly resumes, but undue fluctuations are detrimental to healthcare systems [22] and therefore negatively affect patients. The natural inclination to prescribe reference biologics is then tantamount to 'short-term gain, long-term pain.' To prevent transient reductions in costs of biologics, many institutions have advocated post-launch biosimilar incentivization policies or at least the adoption of active measures that foster healthy competition and sustainable pricing [23, 24]. Otherwise, patients may not benefit from biosimilars' full added value. Healthcare administrations in several European countries, most recently France [25], have taken action along these lines. A grace period for newly launched biosimilars may also encourage fairness in competition. Such balance is vital, given the known preferences for reference biologics and the skewed perceptions of risks attached to biosimilars. If the pharmaceutical companies marketing biosimilars were to withdraw their products from the market, the opportunity

cost would be too high and biosimilars would ultimately lose their fundamental value.

5 Conclusion

Healthcare systems in many jurisdictions provide universal coverage, but the economic implications of therapeutic decisions cannot be ignored. Sustainability demands that clinical judgments be tempered in part by cost restraints. Whereas the merit of original biologics is unquestioned, biosimilars contribute principally to the sustainability of healthcare systems so that present and future patients are properly served. Stakeholders must also acknowledge that the advantages of biosimilars are more than monetary, bolstered by empiric validation throughout Europe since their inception. However, without active healthy competition policies, or incentives for use, the promise of biosimilars is apt to fall short. Nowadays, intervention by healthcare administrations is therefore imperative, in the interest of patient care, to prevent withdrawal of biosimilars from the marketplace. Measures to avoid reference prices, foster switching in patients who are clinically stable, treat naïve candidates, facilitate product procurement (once the biosimilar is available), educate key stakeholders, and more are being adopted in many European countries. The clinical outcomes of these mandates, which bode well for patients, are already apparent.

Compliance with Ethical Standards

Funding No funding was received for the drafting of this review.

Conflict of interest Within the past 5 years, Dr de Mora has served as speaker/consultant for assorted pharmaceutical companies (including Amgen, Biogen, Celltrion, Finox, Gebro, Hikma, Hospira, Kern-Pharma, Lilly, Mylan, Pfizer, Roche, Sandoz, Stada, and Theramex) producing biosimilars or original biologics and for biosimilar company associations. He also collaborates with healthcare administrations and other non-governmental organizations from European and non-European jurisdictions on biosimilar science, regulation, clinical use, and market trends.

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