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Rheumatoid Arthritis (Y Yazici, Section Editor)

New Treatments in Rheumatology: Biosimilars

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Abstract

Purpose of review Biosimilar versions of biologic agents have become increasingly available over the past decade. The framework for regulatory approval has been well established in the USA and Europe, and many biosimilars for use in oncology, rheumatology, dermatology, and inflammatory bowel disease treatment have been approved. Although the utilization of biosimilars has led to substantial cost savings in European countries, this has not occurred in the USA.
Recent findings In this review, we explore several reasons for the limited uptake of biosimilars in the USA. Discounts and rebates to pharmacy benefits managers and patent litigation are major impediments. Furthermore, physicians and patients in the USA continue to express concerns that biosimilars do not have comparable safety and efficacy, despite abundant scientific evidence to the contrary. The Kaiser and Veterans Administration systems have successfully countered these obstacles and achieved dramatic cost savings as a result. The Kaiser experience illustrates the importance of including prescribing physicians as well as patients as stakeholders in the decision to implement use of biosimilars.
Summary However, major changes in the operation of the US health system must also occur for the full potential for cost savings to be realized with use of biosimilars as substitutes for our revolutionary but extremely expensive, biologic medications.

Introduction

As large, complex protein molecules, biologics cannot be exactly duplicated, due to post-translational modifications such as glycosylation and phosphorylation which occur during the manufacturing and

production processes. "Biosimilar" refers to a molecule which is highly similar to a reference product, in contrast to a "generic" which is an exact copy of a synthetically derived small molecule.

The Biologics Price Competition and Innovation Act (BPCIA) was passed in 2010 as part of the Affordable Care Act, to provide an abbreviated licensure pathway for development and approval of competitors to the multiple "biologic agents" which have improved health care in rheumatology, oncology, dermatology, and inflammatory bowel disease treatment [1].The considerable expense of these agents, up to $44,000 annually, poses an enormous financial burden on the health care system [2]. In terms of total spending, the first three available TNF inhibitors (TNFi) rank within the top five most expensive medications in the USA [3]. The potential and need for cost savings are enormous.

Regulatory

FDA considers the "totality of the evidence" when evaluating a biosimilar, to demonstrate that "the biosimilar is highly similar to the reference product.....-with no clinically meaningful differences in safety, purity, and potency (safety and efficacy) from an existing FDA-approved reference product" [4]. Predefined lot-to-lot variability is acceptable; as biosimilars are developed based on multiple lots of the reference product, they typically have tighter specifications and narrower lot-to-lot variability than the reference product. As of 2020, some 22 biosimilars have been approved in the USA, 13 of which are for rheumatology indications (Table 1).

The biosimilar applicant must submit data regarding toxicology in animals based on studies performed with the reference product and must perform one or more clinical trials in one or more of the indications for which the reference

Table 1. FDA-approved biosimilars for rheumatology indications [1]

Biosimilar	Brand name	Manufacturer	Date approved
Infliximab-dyyb	Inflectra	Pfizer/Celltrion	April 2016
Infliximab-abda	Renflexis	Merck/Samsung Bioepis	May 2017
Infliximab-qbtx	Ixifi	Pfizer	December 2017
Infliximab-axxq	Avsola	Amgen	December 2019
Adalimumab-atto	Amjevita	Amgen	September 2016
Adalimumab-adbm	Cyltezo	Boehringer-Ingelheim	August 2017
Adalimumab-adaz	Hyrimoz	Sandoz	October 2018
Adalimumab-bwwd	Hadlima	Samsung	July 2019
Adalimumab-afzb	Abrilada	Pfizer	November 2019
Adalimumab-fkjp	Hulio	Mylan/Fujifilm Kyowa Kirin	July 2020
Etanercept-szzs	Erelzi	Sandoz	August 2016
Etanercept-ykro	Eticovo	Samsung	April 2019
Rituximab-abbs	Truxima	Celltrion/Teva	November 2018
Rituximab-pvvr	Ruxience	Pfizer	July 2019

[1] https://www.fda.gov/drugs/biosimilars/biosimilar-product information

product is licensed to demonstrate biosimilarity including pharmacokinetics, pharmacodynamics, and immunogenicity. Further, the BPCIA stipulates that for a biosimilar to be considered "interchangeable," it is expected to "produce the same clinical result as the reference product in any given patient". [4] Once approved, an interchangeable product could be substituted for the reference product without knowledge of the prescriber. For the FDA to define a biosimilar as interchangeable, a study that includes at least 3 switches between biosimilar and reference product must be performed demonstrating equivalent PK, PD, immunogenicity, and efficacy as well as comparable safety [4]. However, there are laws in 45 states that prevent such substitution [5]. No such designation exists elsewhere in the world.

The European Medicines Agency (EMA) has been regulating biosimilars since 2005 and also includes insulin among designated biologic reference products. Some 47 biosimilars have been approved by EMA; requirements for approval are very similar to those outlined in the USA and provide specific guidelines for individual categories of biosimilars, e.g., monoclonal antibodies, insulin, somatostatin, and G-CSF [6]. Differences include that EMA requires brand naming of biosimilars, whereas in the USA, a biosimilar is identified by a four letter suffix following the scientific name [7] and that EMA requires a specific post-marketing surveillance plan whereas this is not necessary in the USA if the requirements for the reference product have already been satisfied [6].

Characterization of biosimilars

Biosimilars must be characterized based on primary structure, functional assays, and critical quality attributes (CQAs) [8]. The primary sequence of the reference product is known from its patent; its manufacturing processes and characterization are proprietary information: the type of host cell, conditions of culture, post-translational modifications, and purification of the final product. The primary structure must be identical; integrity of the secondary, tertiary, and quaternary structures must be demonstrated to be highly similar. Functional assays must demonstrate highly similar receptor binding, immunochemical properties, and kinetics and thermodynamics of binding to antigen, Fc receptor binding, and effector functions such as ADCC and CDC. These CQAs pertain to the identity, purity, biological activity, and stability of the biosimilar and are classified into three tiers, according to their potential impact on clinical activity

Comparison studies of biosimilar to reference product

A single dose trial in healthy volunteers comparing biosimilar to both US-produced and ex-US produced reference products is required by the FDA to demonstrate that pharmacokinetics and immunogenicity are equivalent for maximum serum concentration and area under the time-concentrations curves [6].

In addition, a head-to-head clinical trial comparing biosimilar to reference product must be performed in at least one clinical indication for which the reference product is approved [4].

A trial demonstrating equivalence of a biosimilar to reference product (regardless of where it was manufactured) allows extrapolation of use of that biosimilar to all the clinical indications for which the reference product is approved [7].In general, these trials are based on the design of the pivotal trials that supported approval of the reference product [8].

The possible consequence of switching from reference product to biosimilar must be carefully addressed in studies [9]. Most studies include a single switch from reference product to biosimilar; multiple switch trials are required to gain FDA approval for the "interchangeability" designation. [6] Such trials have been performed for etanercept-szzs (Sandoz) and adalimumab-adbm (Boehringer Ingelheim), although no formal approvals have yet been granted [10].

Immunogenicity

The testing for immunogenicity of a biosimilar yields different data than known for the reference products, given that assays currently in use are much more sensitive as well as drug tolerant than those used at their initial approvals. In these earlier tests (ELISA or RIA), serum levels of the monoclonal antibodies or soluble receptors would often interfere with the assays. Newer methods, such as electrochemiluminescence (ECLIA) or flow-through microfluidic immunoassays, are therefore performed after acid dissociation of the drug and antidrug antibody (ADAb) complexes [11].

In a guidance document issued in April 2016, the FDA defined immunogenicity as "the propensity of the therapeutic protein product to generate immune responses to itself and to related proteins or to induce immunologically related adverse clinical events" and made specific recommendations regarding assay development for detecting ADAbs [11]. Another guidance document in May 2019 stipulated that products with a "documented history of inducing detrimental immune responses may require more data than products with an extensive documented history that immunogenicity does not impact clinical outcomes." [4]. Overall, the degree of immunogenicity between biosimilars and their reference products is similar, but typically higher than demonstrated for the reference product at the time of approval, due to more sensitive drug tolerant assays now in use [12]. There is consensus that measurement of ADAbs in rheumatology clinical practice is not typically indicated, since there cannot be significant differences in immunogenicity between biosimilar and reference products. However, one must consider that infliximab, rituximab, and adalimumab are more likely than other biologics to generate ADAbs which may lead to loss of response over time.

Economic impact in Europe

Since the first biosimilar was approved in 2006, Europe has been at the vanguard of the biosimilar medicines sector, approving more treatments over the last 15 years than anywhere else in the world. Substantial cost savings have been achieved by switching to biosimilars, as will be discussed below. Over the last 5 years, usage has significantly increased, and biosimilars have challenged the established order of care [13]. EMA does not regulate switching or substitution of a reference product by a biosimilar medicine, leaving it to individual

member states, health authorities, and payers to determine. Utilization of biosimilars in Europe is very broad but varies from country to country as they take different approaches in how they procure medications and negotiate prices, leading to variability in adoption of biosimilars [14].

Minimal use to date in us

Although the Rand Corporation has estimated that biosimilars could save the US health system $54 billion over a decade, usage in the USA has lagged far behind Europe [15]. Generic small molecule drugs represent 90% of all prescriptions in the USA, having generated substantial savings. Biologics represent almost 40% of all prescription drug spending and accounted for 70% of growth in drug spending from 2010 to 2015; yet biosimilars have not had a substantial impact reducing costs.

Biosimilars for infliximab, adalimumab, etanercept, and rituximab have been approved by the FDA. Biologics account for $120 billion (37%) of net drug spending, despite representing only 2% of all prescriptions written in the USA. Furthermore, since 2014, biologics are responsible for 93% of the overall growth in total spending [16]. A recent study from Johns Hopkins reported to the ERISA Industry Committee that the infliximab biosimilar price represented 68% of the reference product, and patients who received the biosimilar paid, on average, 12% less out-of-pocket. The report also noted that self-insured companies could have saved $407 million to $1.4 billion in 2018 if they had switched completely from reference infliximab and filgrastim to biosimilars. The study also estimated potential savings for Medicare programs at $279 million in 2018 [17].

In August 2018, the FDA published its Biosimilars Action Plan (BAP) to encourage Biosimilar competition. "One of FDA's less appreciated roles is to take responsibility for implementing laws intended to strike a balance between encouraging and rewarding innovation in drug development and facilitating robust and timely market competition" [18]. The BAP was developed to supplement the process articulated in the BPCIA with the idea *that biosimilars could be positioned to create substantial cost savings* (our emphasis).

A recent study of a large insurance data base (~1.1 million total TNFi prescriptions or infusions dispensed to 95,906 unique patients) showed <1% uptake of biosimilar infliximab. The authors conclude "that in the USA, current savings are insufficient to promote the widespread use of infliximab biosimilars, and savings comparable with those achieved in some European countries may not be possible without systemic reform of the US pharmaceutical market" [19]. Another study of Medicare patients showed no significant reduction in out-of-pocket costs for patients receiving biosimilar infliximab [20].

A large study in Philadelphia examined use of infliximab and filgrastim, reference products, and biosimilars, comparing results at an academic medical center and a VA hospital. There was much greater utilization of biosimilar infliximab at the VA (38%) than the university hospital (1%), primarily because the use of the biosimilar was mandated at the VA [21]. There are likely other important factors to explain the limited use of biosimilars at the university hospital, as will be discussed below.

Uptake of biosimilars in the USA has been greatly limited by economic, legal, and other factors. While it seems intuitive that they would be less expensive and therefore offer a cost advantage, this is not the case given the exigencies of the US health insurance system. The first issue is reimbursement, which relates to the Average Sales Price (ASP). Reimbursement for Medicare Part B is set at 104.3% of ASP; the higher the ASP, the higher the reimbursement. A biosimilar with a lower ASP would therefore result in a lower reimbursement than a reference product with a higher ASP. In many cases, the sponsor with a reference product has more room to negotiate than the biosimilar sponsor, thus reducing the financial incentive [22]. On the other hand with the 340B drug discount program, biosimilars are treated as innovator products and accorded "pass through status"; this means that 340B hospitals are reimbursed at ASP plus 6% rather than ASP minus 22.5% for the reference product. This actually incentivizes 340B hospitals to utilize biosimilars to obtain higher payments than for reference products [23].

Another extremely important issue is the so-called rebate trap. Pharmacy benefits managers (PBMs), which distribute these medications for insurance companies, can obtain substantial rebates for utilizing a reference product. If the contracting stipulates that the PBM gives preference for dispensing the reference product, the rebate would be lost if the biosimilar were dispensed. Therefore, the PBM is in the position of having a vested financial interest in continuing to dispense the reference product, as the rebate amount can easily outweigh the lower retail price for a biosimilar [24].

Pfizer filed a lawsuit against Johnson & Johnson alleging that its contracts with health insurers for infliximab (Remicade) were anticompetitive by offering discounts to health insurers, hospitals, and doctor's groups, which interfered with sales of biosimilar Inflectra: infliximab-dyyb. The suit further claims that these exclusionary contracts were signed in 2016 after the biosimilar was approved and that after-market rebates provide even more incentive for use of reference product infliximab [25].

In September 2018, a motion to dismiss was denied by the US District Court of the Eastern District of Pennsylvania [26]. Johnson & Johnson has also been sued by Walgreens and Kroger for antitrust violations, citing its contracts with wholesale distributers. Although the case was initially dismissed, the Third Circuit ruled on appeal that the case was valid because of its focus on federal antitrust law and referred it back to the lower courts [27]. A Civil Investigative Demand was issued in June 2019 to Johnson & Johnson by the Federal Trade Commission (FTC) regarding its contracting practices. It is possible that this inquiry could lead to an antitrust determination depending on the results of the investigation.

The Philadelphia study above illustrates another barrier. Medicare is not allowed to negotiate with industry regarding the price of product [28], whereas the VA system, the largest single health care system in USA, does have that power with its centralized negotiation and contract management and has mandated switching patients to less expensive biosimilars in some cases [29]. The VA system, but not Medicare, has a strong financial incentive to utilize less expensive medications and has made a major effort to utilize biosimilars for financial savings. In 2017, the VA system adopted Inflectra: infliximab-dyyb (Celltrion/Pfizer), but in 2018, it switched to Renflexis: infliximab-abda (Samsung Bioepis/Merck) because of a lower price [30]. It has been estimated that, had Medicare negotiated in a similar fashion, it would have saved $14.4 billion in 2015 [31].

Legal issues related to patents have been a major obstacle to biosimilar uptake in the USA. Pharmaceutical companies have asserted extensive patient infringements to delay the release of biosimilars after expiration of the 12-year market exclusivity periods granted to the originators by BPCIA. However, the patents for the molecules, manufacturing, and therapeutic uses are in force for 20 years after they have been issued. BPCIA provides a mechanism to resolve patent disputes between reference product and biosimilar applicants, similar to the Hatch-Waxman Act for synthetic generics [32].

For example, two etanercept biosimilars have been approved in the USA: Erelzi: etanercept-szzs (Sandoz) and Eticovo: etanercept-ykro (Samsung Bioepis) but have yet reach the marketplace. Amgen brought suit against Sandoz for infringing five patents (issued between 1995 and 2009) to covering the fusion protein, manufacturing methods and therapeutic uses [33]. In 2019, the judge in US District Court for the District of New Jersey found in favor of Amgen [34]. Sandoz is expected to appeal. Immediately after etanercept-ykro was FDA-approved in April 2019, Amgen filed a similar lawsuit against Samsung Bioepis [35].

AbbVie has filed over 200 patents regarding the molecule adalimumab, manufacturing methods, and therapeutic uses, half of which were filed after expiration of the 12-year exclusivity in 2014 [36]. Similarly, AbbVie has settled with Boehringer Ingelheim for Cytelzo: adalimumab-adbm which will launch in January 2023.

Patent disputes have also delayed the availability of Truxima: rituximab-abbs (Celltrion (Korea) and Teva Pharmaceuticals, Ltd.). In January 2018, suits were filed regarding Genentech patents for methods of growing mammalian cells in vitro, protein purification, and dosing. Celltrion and Teva claimed that Genentech asserted a "panoply of vague allegations…simply intended to interfere with Celltrion and Teva's entry into the market." In November 2018, the parties settled [37], allowing the marketing of the biosimilar only for oncology indications, despite a 24-week equivalence RCT comparing it to rituximab in patients with active RA [38]. Sandoz has also been in litigation with Genentech over another biosimilar, but Sandoz has decided to discontinue its rituximab program. Another biosimilar, Ruxience: rituximab-pvvr, was approved in the USA in 2019 after Pfizer settled another patent dispute with Genentech. As with the Celltrion BS, it was studied in RA, comparing its PK and immunogenicity to US and ex-US manufactured rituximab. However, it did not gain approval in RA, only for GPA, MPA, and oncology indications [39].

The United Food and Commercial Workers Local 1500 has filed a class action lawsuit against AbbVie, arguing that efforts have been made to prevent emergence of biosimilars by using patents, noting that over 100 patents have been used to delay biosimilars from reaching the marketplace before 2023. The suit also alleges that AbbVie provided financial inducements to biosimilar competitors to delay the launch of their products in the USA [40].

In July 2018, a new Office of Therapeutic Biologics and Biosimilars (OTTB) was created by the FDA Biosimilars Action Plan to coordinate and improve activities under the Biosimilar User Fee Act (BSUFA) and to promote the Biosimilar Outreach and Education Campaign (BOEC) to educate health professionals [41]. It was noted that the FDA would show leadership in highlighting practices which create "an imbalance between innovation and competition," to address matters such as discussed above. Four key goals of the BOEC are to:

(1) Improve the development and approval process for biosimilars
(2) Maximize scientific and regulatory clarity
(3) Improve communication regarding biosimilars to health care providers
(4) "Support market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition" (our emphasis)

The Biologic Patent Transparency Act is a proposed legislation with bipartisan support to limit "competition-stymieing patent thickets that delay competition" when such patents are issued after a biosimilar has been submitted to the FDA. The FDA has recently made efforts to address the means by which biosimilars are presented to the general public in advertising [42]. A new FDA guidance entitled "Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products: Questions and Answers" has recently been published to address issues by which companies present biosimilars and reference products in promotional materials [43]. In fact, the FDA has been interacting with the Federal Trade Commission (FTC) to address these issues. Specifically, the guidance addresses "representation or suggestions that create an impression that there are clinically meaningful differences between the reference product and its biosimilar, such as promotional presentation representing or suggesting that a reference product is safer or more effective than its biosimilar product…are likely to be false or misleading" [44].

Another issue which might contribute to the reluctance of US physicians and patients to adopt biosimilars is "switching," changing from the reference product or even switching back and forth between biosimilars and their reference products. Switching to reduce costs is referred to as "non-medical switching." A 2019 survey showed that 84% of the US physicians would oppose switching a stable patient from reference product to biosimilar [45].

In other countries, there is greater interest in cost savings, in part because they have been dramatically demonstrated. At least 4 of Canada's 10 provinces plan to switch patients from reference products to save money. Alberta projects a savings of $268 million (US) over the next 4 years. The province will have switched at least 26,000 patients by the summer of 2020 [46].

The Norwegian government in 2013 commissioned NOR-SWITCH, a randomized controlled trial including 498 stable patients receiving infliximab (Remicade) for at least 6 months for treatment of RA, spondyloarthropathy, psoriatic arthritis, psoriasis, or ulcerative colitis. Enrollees were randomized to either continue infliximab (Remicade) or switch to the biosimilar Remsima (Celltrion). NOR-SWITCH showed non-inferiority across all clinical indications but was not powered to assess efficacy in specific diagnoses [47].

The Danish government mandated a "non-medical switch" from etanercept to Eticovo: etanercept-ykro in 2016 because of price [48]. Seventy-nine percent of 2061 reference product-treated patients switched to biosimilar with no change in disease activity over 3 months. In this longitudinal study at one year, 83% of "switchers" remained on the biosimilar compared with a historic cohort with 90% retention. The retention rate in "non-switchers" was actually lower at 77%. However, further analysis showed that the switch group had longer etanercept treatment and fewer previous bDMARDS than the non-switchers and perhaps had milder disease [49]. Seven percent of "switchers" switched back to reference product for reasons the investigators considered "subjective."

A factor which potentially influences the perspective of patients and physicians regarding switching is the "nocebo effect": a negative expectation influenced by the fear or aversion of switching to a biosimilar that could influence perception on the part of patient or doctor that the changed medicine is less effective or more toxic [50]. In several studies there has been a greater reporting of adverse events and patient discontinuations attributed to the "nocebo effect" [51–53]. Just as the placebo effect may result in perceived benefit when no medication is given, the nocebo effect can result in the patient and/or physician concluding that a switch from reference product to biosimilar is less effective or tolerated. There are data suggesting that if the patient fears that the biosimilar might not be as safe or effective as the reference product, this could influence their perception of their experience in a negative direction.

The Kaiser Health Plans have achieved dramatic uptake of multiple biosimilars, and their success provides a strategy to mitigate the nocebo effect. A major factor was their decision to decline rebates, which totally changed the financial calculation. Furthermore, they proactively addressed concerns that physicians might have about switching. This highly integrated health plan takes an evidence-based approach to formulary decisions, involving stakeholder physicians. Sameer Aware, MD, Associate Executive Director, The Permanente Medical Group, noted that "the oncology doctors were ready to move to bevacizumab when (it) launched," with 97% uptake of the bevacizumab biosimilar in only one month. He attributes that success to involving oncologists in the decision to make the switch, so that this decision had credibility with prescribing physicians. Amy Gutierrez, PharmD, Senior Vice President and Chief Pharmacy Officer, believes that they can achieve biosimilar uptake of 80 to 95% because Kaiser has the ability to get "immediate P&T decisions and put coverage in place rapidly. Ninety-five percent of the patients taking infliximab are receiving infliximab-dyyb, launched late in 2017. As of November 2019, Kaiser has saved approximately $200 million since covering its first biosimilar [54]. Like the VA, Kaiser has focused on financial savings as the motivating factor for embracing biosimilars. In response to some GI physicians who were concerned that infliximab biosimilars might not be safe, Kaiser started a registry to address concerns. However, there was no evidence of a difference in safety or efficacy in a 54-week study switching inflammatory bowel disease patients from Remicade to infliximab-dyyb biosimilar [55].

Just as cost savings has motivated Kaiser and the VA, there is potential benefit to employers to promote the use of biosimilars. It has been estimated that 40–50% of health insurance spending for employees is for specialty medications. Employers actually have a greater potential to obtain cost savings than the health plans, since the latter can take advantage of discounts and rebates [56].

Conclusion

In the past decade, biosimilars have been developed for many reference biologic products. The scientific assessments, manufacturing processes, and clinical trials have been mastered, and the regulatory requirements while slightly different between FDA and EMA have ensured their efficacy and safety. In Europe, huge cost savings have been achieved as a result of switching to biosimilars. However, similar uptake has not been achieved in the USA, despite that biosimilars should

deliver substantial costs savings. The reference product sponsors have utilized rebates and discounts to provide a financial interest to PBMs to continue the use of their products—even at greater cost. The Kaiser and VA systems are examples of systems which have taken aggressive action to utilize biosimilars with resultant huge cost savings. Furthermore, legal challenges claiming patent infringement have delayed utilization of biosimilars in the USA long after FDA approval. Finally, considerable education of physicians and patients remains necessary to further the general perception that biosimilars are truly safe and effective. All of these issues will have to be successfully addressed before we are able to achieve substantial cost savings through extensive use of biosimilars.

Compliance with ethical standards

Human and animal rights
This article does not contain any studies with human or animal subjects performed by any of the authors.

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