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The First 2 Years of Biosimilar Epoetin for Cancer and Chemotherapy-Induced Anemia in the U.S.: A Review from the Southern Network on Adverse Reactions

Charles L. Bennett,[a,b] Sumimasa Nagai,[c] Andrew C. Bennett,[b] Shamia Hoque,[d] Chadi Nabhan,[b] Martin W. Schoen,[e] William J. Hrushesky,[b] Stefano Luminari,[f,g] Paul Ray,[b] Paul R. Yarnold,[b] Bart Witherspoon,[b] Josh Riente,[h] Laura Bobolts,[i,j] John Brusk,[j] Rebecca Tombleson,[b,j] Kevin Knopf,[b] Marc Fishman,[b,i] Y. Tony Yang,[k] Kenneth R. Carson,[l] Benjamin Djulbegovic,[m] John Restaino,[b] James O. Armitage,[n] Oliver A. Sartor[o]

[a]Toni Stephenson Lymphoma Center, the Hematologic Malignancies Research Institute, the Beckman Research Institute, of the City of Hope Cancer Center, Duarte, California; [b]College of Pharmacy and [d]Civil and Environmental Engineering, College of Engineering and Computing, University of South Carolina, Columbia, South Carolina; [c]The University of Tokyo Hospital, Tokyo, Japan; [e]Saint Louis University School of Medicine, Saint Louis, Missouri; [f]Hematology, AUSL IRCCS Reggio Emilia; [g]Department CHIMOMO, University of Modena and Reggio Emilia, Regio Emilia, Italy; [h]William J Bryan Dorn Veterans Administration Medical Center, Columbia, South Carolina; [i]Oncology Analytics, Atlanta, Georgia; [j]College of Pharmacy, Nova Southeastern University, Fort Lauderdale, Florida, USA; [k]George Washington University School of Nursing and Milken Institute School of Public Health, Washington, DC; [l]The Division of Hematology/Oncology, Department of Medicine, Rush University School of Medicine, Chicago, Illinois; [m]The City of Hope, Beckman Research Institute, Department of Computational and Quantitative Medicine, Division of Health Analytics, Evidence-based Medicine & Comparative Effectiveness Research, Duarte, CA; [n]The Department of Medicine, The University of Nebraska School of Medicine, Omaha, Nebraska; [o]The Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana

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Key Words. Epoetin • Biosimilars • Interchangeable • Substitution • Guidelines

Abstract

Biosimilars are biologic drug products that are highly similar to reference products in analytic features, pharmacokinetics and pharmacodynamics, immunogenicity, safety, and efficacy. Biosimilar epoetin received Food and Drug Administration (FDA) approval in 2018. The manufacturer received an FDA nonapproval letter in 2017, despite receiving a favorable review by FDA's Oncologic Drugs Advisory Committee (ODAC) and an FDA nonapproval letter in 2015 for an earlier formulation. We discuss the 2018 FDA approval, the 2017 FDA ODAC Committee review, and the FDA complete response letters in 2015 and 2017; review concepts of litigation, naming, labeling, substitution, interchangeability, and pharmacovigilance; review European and U.S. oncology experiences with biosimilar epoetin; and review the safety of erythropoiesis-stimulating agents. In 2020, policy statements from AETNA, United Health Care, and Humana indicated that new epoetin oncology starts must be for biosimilar epoetin unless medical need for other epoetins is documented. Empirical studies report that as of 2012, reference epoetin use decreased from 40%–60% of all patients with cancer with chemotherapy-induced anemia to <5% of such patients because of safety concerns. Between 2018 and 2020, biosimilar epoetin use varied, increasing to 81% among one private insurer's patients covered by Medicare whose cancer care is administered with Oncology Analytics and to 41% with the same private insurer's patients with cancer covered by commercial health insurance and administered by the private insurer, to 0% in several Veterans Administration Hospitals, increasing to 100% in one large county hospital in California, and with yet-to-be-reported data from most oncology settings. We conclude that biosimilar epoetin appears to have overcome some barriers since 2015, although current uptake in the U.S. is variable. Pricing and safety considerations for all erythropoiesis-stimulating agents are primary determinants of biosimilar epoetin oncology uptake. ***The Oncologist*** 2021;26:e1418–e1426

Implications for Practice: Few oncologists understand substitution and interchangeability of biosimilars with reference drugs. Epoetin biosimilar is new to the market, and physician and patient understanding is limited. The development of epoetin biosimilar is not familiar to oncologists.

Correspondence: Charles L. Bennett, M.D., College of Pharmacy, University of South Carolina, Coker Life Sciences Building, 773 Sumter Street, Columbia, South Carolina 29208, USA. Telephone: 803-777-9004; e-mail: bennettc@cop.sc.edu. Received August 7, 2020; accepted for publication January 5, 2021; published Online First on March 12, 2021. http://dx.doi.org/10.1002/onco.13713

Introduction

Biosimilar drugs, close copies of patented biologicals, are intended to provide access to less expensive, highly similar versions of approved reference biological agents [1]. The biological epoetin accounts for $1.8 billion in drug spending annually worldwide, primarily for treatment of anemia due to chronic kidney disease or cancer chemotherapy.

Mature epoetin biosimilar markets have existed in European Union (EU) countries since 2007, as five epoetin biosimilar formulations have received regulatory authorizations in EU countries [2, 3]. Biosimilar epoetins account for 45% of EU epoetin sales (varying by country) [3, 4]. Similarly, oncology biosimilar uptake in the U.S. for filgrastim was rapid, accounting for 52% market share at 18 months. Herein, we review the development of the first epoetin biosimilar in the U.S. and compare its use with that of biosimilar epoetins in Europe and biosimilar filgrastim in the U.S.

Search Strategy and Selection Criteria

We reviewed relevant peer-reviewed articles with use of MEDLINE (PubMed), Embase (Ovid), and Web of Science. Search terms included "erythropoietin," "biosimilars," "follow-on biologics," "similar biologic products," "subsequent entry biologics," "follow-on biologic products," and "similar biologic medicinal products." The search was restricted to papers published between January 2005 and January 2021, in English or Japanese, and comments, editorials, journal articles, reviews, or systematic reviews addressing biosimilar epoetin. Additional non-peer-reviewed literature was included in this review and identified through a Google search and from citations in several key articles.

Results

Regulatory Approval for Epoetin Biosimilar in the U.S.

The Biologic Price Competition and Innovation Act of 2009, enacted as part of the Affordable Care Act in 2010, created an abbreviated licensure pathway for biosimilars [the 351 (k) pathway; Table 1]. These regulations require demonstration of a high degree of "similarity" of a biosimilar with reference biologic—comparing physiochemical and immunochemical properties, biological activity, specifications, stability, safety, and efficacy [1]. The "totality of the evidence" supports regulatory approval [1]. The process is based on a step-wise approach, with the applicant characterizing and evaluating residual uncertainty at each step. The underlying rationale is that a biologic product that is shown to be analytically and functionally similar to a reference product is anticipated to behave like the reference product in the clinical setting. This approach begins with demonstration of structural and functional characterization of the proposed biosimilar and the reference biologic. Once analytical similarity is demonstrated, an assessment is made of the amount of residual uncertainty with respect to structure/function characterization and the potential for clinically meaningful differences. In contrast to European Union requirements, the Food and Drug Administration (FDA) requires animal in vivo studies to be conducted and stipulates that the reference biologic must be a U.S.-approved product.

In May 2018, the FDA approved biosimilar epoetin for marketing in the U.S., although it became commercially available in November 2018. In 2017, the Oncology Drug Advisory Committee of the FDA reviewed the application of Hospira (the biosimilar sponsor) for an epoetin biosimilar and recommended by a 14 to 1 vote that the FDA grant regulatory approval of the biosimilar for the same clinical indications as those the FDA had previously granted for the reference biologic epoetin alfa (manufactured by Amgen). Despite this recommendation, the FDA issued a complete response letter 1 month later denying FDA approval of the product for manufacturing reasons. In 2015, a complete response letter was also received by the sponsor with the primary reason being a 3.5% difference in mean content between reference and biosimilar epoetin. In 2017, the FDA overruled its Oncology Drug Advisory Committee, citing manufacturing problems at potential manufacturing sites and not granting regulatory approval. The FDA had previously issued warning letters about the same plants (FDA Complete Response Letters to Hospira May 15, 2015, and June 2017) [5, 6].

Chemistry, Manufacturing, and Controls

Endogenous erythropoietin (EPO), produced mainly by the kidney, stimulates erythropoiesis. EPO binds to EPO receptors on lineage-committed erythroid progenitor cells, initiating signal transduction that results in proliferation and differentiation into red blood cells. Pharmacodynamical measures of this effect include reticulocyte count and serum hemoglobin levels. Epoetin alfa is a 165-amino acid recombinant protein that has the same amino acid sequence as endogenous EPO [7].

Epoetin biosimilar was compared with reference epoetin with several physiochemical and functional methods. Amino acid sequences of the two products were the same. Glycosylation, a post-translational modification necessary for protein function and stability, occurred at the same specific arginine and serine-residue sites. However, composition of the glycans is complex, varies among different EPO products, and is attributed to manufacturing process differences. Glycosylation contributes to pharmacokinetics (PK) of endogenous and recombinant EPO, mainly by increasing EPO's half-life. Residual differences between biosimilar and reference epoetin were noted in glycosylation [8].

Epoetin biosimilar is produced in Chinese Hamster Ovary cells transfected with the human EPO gene [8]. The manufacturing process is made up of various steps intended to isolate and purify EPO. The sponsor demonstrated that process-related impurities, including host cell proteins, host cell DNA, and host retrovirus-like particles, were reduced to low levels in the manufacturing process. The product was developed as a liquid injection filled in single-use vials at the same strengths as those approved for the reference epoetin.

Table 1. Key characteristics of biosimilar epoetin in the U.S.

Year of final regulatory approval	2018
Regulatory approval studies	The 2018 FDA approval was based in part on the results of two randomized, double-blinded, parallel group clinical trials that enrolled patients with chronic kidney disease on hemodialysis who were receiving epoetin maintenance treatment with coprimary endpoints of differences between arms in mean weekly hemoglobin levels and mean weekly dose. One study (EPOE-10-13) evaluated 246 patients who received subcutaneous drug one to three times per week. The other study (EPOE-10-01) evaluated 612 patients who received intravenous drug three times per week. Overall, 121 unique study sites participated in these trials. Safety assessments did not identify significant differences between the products. Efficacy analyses reported that 90% confidence intervals for the outcome values were within the predetermined equivalence margins [8].
Regulatory review criteria [5]	Biosimilar epoetin specific. Stepwise analytic approach.
No. of marketed epoetin biosimilars	1
Regulatory review (biosimilar vs. biologic pathway)	Biosimilar (351k pathway)
Market approval date	May 2018
Regulatory review times	12 months (including time to respond to a complete response letter)
Originator main patent expiration	2015
Patent litigation between reference and biosimilar sponsor	In a completed case in federal court, Amgen claimed that the FDA-approved biosimilar epoetin alfa product infringed on two patents while conducting licensing clinical trials (U.S. Patent Nos. 5,856,298 and 5,756,349), one of which covers several EPO isoforms and their selection processes, whereas the other protects proprietary cell lines to manufacture epoetin. The jury awarded $70 million in favor of Amgen. Hospira's appeal was denied.
Most recent biosimilar naming convention	2017
Naming	Epoetin alfa plus four-letter suffix is the nonproprietary name (Epoetin alfa-epbx). The commercial name is Retacrit.
Labeling	The labels for reference and biosimilar epoetin are similar.
Guidelines	The 2019 ASCO/ASH Guideline's recommendation 5 indicates that the panel considered all erythropoiesis-stimulating agents to be equivalent based on informal consensus but judging that evidence was of intermediate quality (meaning that the panel had moderate confidence that the available evidence reflects the true magnitude and direction of the net effect) [27].
Substitution	Forty-five states have passed legislation against pharmacy substitution. Some states will allow substitution if the interchangeability has been designated by the FDA [16].
Interchangeability	FDA guidance on this topic was finalized in 2018. To date, no biosimilar in the U.S. is designated as an interchangeable biosimilar.
Determinants of price setting	Set by federal health programs and with individual health insurers. Rebates are common.

Abbreviations: ASCO/ASH, American Society of Clinical Oncology/American Society of Hematology; EPO, erythropoietin; FDA, Food and Drug Administration.

Formulations of the two epoetin products differ with respect to inactive ingredients and pH. The material used in nonclinical studies was manufactured using processes that differed from the final commercial process with respect to EPO content. In 2017, FDA reviewers agreed that the biosimilar epoetin manufacturing processes were valid and produced a product of consistent quality and that formulation differences did not have clinical effects.

Analytical similarity data have been evaluated. Independent analyses of these data and associated statistical analyses were reported by FDA reviewers in 2017. Reference epoetin contains human serum albumin at concentrations that interfered with chemical analysis by several methods. The sponsor developed procedures for removing human serum albumin to facilitate analytical comparisons in settings where this did not impact specific quality attributes. These studies evaluated primary structure, glycosylation, higher order structure, biological activity, drug product attributes, and product-related substances and impurities. It was noted that a 2015 marketing application of a biosimilar epoetin from the same sponsor using a different commercial process found a 3.5% difference in mean EPO content. This difference was attributed to a manufacturing issue, which was addressed after the 2015 submission.

Biological Activity

Biological activity was evaluated using assays directed to EPO's mechanism of action, focusing on EPO receptor binding, cell proliferation induction, and reticulocyte production. Tests included a competitive receptor binding enzyme-linked immunosorbent assay, surface plasmon resonance measurement, an in vitro cell-based bioassay using a human leukemic cell line (UT-7), and a compendial-based in vivo normothymic mouse assay (mice reticulocyte production

was measured) [9]. In 2017, statistical equivalence analyses for in vitro and in vivo studies were assessed by FDA reviewers as being within the acceptance criteria and within the accepted quality range defined based on the reference biologic. FDA reviewers concluded that these data supported a conclusion of biosimilar biological activity. Glycosylation differences in the two products did not result in observable differences in mouse biological activity. Seven comparisons of the type and levels of product-related substances and impurities in the products supported conclusions of high similarity [10]. Biosimilarity was also demonstrated with respect to subvisible particles, which are implicated as potential causes of antiproduct antibodies using microflow imaging and nanoparticle tracking analyses.

Pharmacology/Toxicology

The products were compared in two head-to-head 13-week animal studies assessing pharmacodynamics (PD), pharmacokinetics (PK), and toxicity in rats and dogs [10]. Some comparisons could be evaluated only in beagle dogs with intravenous administration. Although there were residual uncertainties in the two products based on nonclinical data, observed differences did not have apparent effects on PK/PD similarity and comparative clinical studies. The sponsor and FDA reviewers noted that recombinant epoetin protein is not species specific, and therefore, animal toxicology studies were relevant to predicting potential human effects. Again, the sponsor and FDA reviewers concluded that there were residual uncertainties as to the PK/PD similarity of the biosimilar in rats and dogs, which needed to be addressed in PK/PD studies in humans and in comparative clinical studies.

Immunogenicity

This topic was extensively discussed and reviewed at the 2017 Oncology Drug Advisory Committee meeting. Studies by Casadevall et al. in 2002 and Bennett et al. in 2004 had identified clinically significant cases of antierythropoietin antibody-mediated pure red cell aplasia (PRCA) with subcutaneous administration of the Eprex formulation of epoetin [2, 11]. In 2010, two cases of antierythropoietin antibody-mediated PRCA had been identified with subcutaneous administration of the same biosimilar epoetin formulation that was approved by the FDA in 2018 [12]. These cases were identified as part of a phase III trial with subcutaneous administration of epoetin alfa to patients with chronic kidney disease (CKD). Root cause analyses, which identified tungsten leaching from syringe pins, and manufacturing process changes fixed this problem. The incidence of immunogenicity for the two products was compared in three multiple-dose, parallel arm studies of 849 patients with CKD and 129 healthy volunteers. No neutralizing antidrug antibodies were identified, and no apparent impact of antidrug antibodies on safety, PK, or PD endpoints were observed.

Clinical Pharmacology

The biosimilar sponsor conducted randomized open-label crossover studies among 81 healthy subjects comparing PK, PD (reticulocyte count in one study and hemoglobin levels in another study), safety, and tolerability of a single 100 U/kg subcutaneous dose of the two products and one randomized open-label parallel group study (EPOE-14-01) of 129 healthy subjects receiving 100 U/kg three times per week subcutaneously [10]. The results were interpreted by the sponsor and FDA reviewers as supporting conclusions of no clinically meaningful differences in PK and PD.

Clinical Efficacy and Safety

The 2018 FDA approval was based in part on results of two randomized, double-blinded, parallel group clinical trials that enrolled patients with chronic kidney disease on hemodialysis who were receiving epoetin maintenance treatment with coprimary endpoints of differences between arms in mean weekly hemoglobin levels and mean weekly dose. One study (EPOE-10-13) evaluated 246 patients who received subcutaneous drug one to three times per week. The other study (EPOE-10-01) evaluated 612 patients who received intravenous drug three times per week. Overall, 121 unique study sites participated in these trials. Safety assessments did not identify significant differences between the products. Efficacy analyses reported that 90% confidence intervals for the outcome values were within the predetermined equivalence margins [10].

Risk Evaluation and Mitigations Strategy (2010–2017)

On February 16, 2010, the FDA announced the approval of a new Risk Evaluation and Mitigation Strategy (REMS) for erythropoiesis-stimulating agents (ESAs) [13]. The ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program became part of the overall REMS and was oncology specific; the APPRISE program only applied to ESAs when prescribed for patients under FDA-approved cancer indications. The major elements of the REMS for oncology included a physician educational module; physician enrollment; dispensation of medication guide to each patient at initiation of each course of therapy and monthly thereafter; physician review of medication guide with patient; physician assistance to patient in completing acknowledgment form; patient signature on acknowledgment form in presence of physician; physician also signs; a copy of the acknowledgment form was provided to the manufacturer; and the original was filed in location separate from patient medical record. The forms were maintained for auditing by the manufacturer; the manufacturer estimates the amount of drug expected to be used by the practice/physician based on the number of forms filed and, for monitoring purposes, compares the estimate with records of actual drug received. The physician attested to understanding FDA-approved indications for ESAs. There was no requirement that patients enroll in a centralized registry, although the manufacturer received copies of acknowledgment forms of all patients receiving the drug. Enrollment in the APPRISE program began March 24, 2010. Providers had a grace period of up to 1 year, at which point they will no longer be eligible to prescribe ESAs without enrolling in the APPRISE program. The policy response of the American Society of Clinical Oncology was that the program was unnecessarily burdensome; that no stakeholder input (from oncologists, patients, or interested members of the publica) had been solicited

during REMS development; and that overall, REMS programs were inconsistent across different branches of FDA and among drugs.

In 2017, FDA reviewers noted that the 2010 requirement for a REMS program for ESAs in the oncology setting ended in April 2017. It had been determined by the FDA that REMS were no longer needed to ensure that ESA benefits outweighed their risks [14]. The FDA made this determination based on evaluation of results of two unpublished REMS Assessments submitted by Amgen, Inc., and additional FDA analyses. The AMGEN Assessment consisted of a prescriber survey and a drug utilization data analysis. The prescriber survey demonstrated acceptable knowledge of ESA risks of decreased survival and/or the increased risk of tumor progression or recurrence and the need to counsel patients about these risks. Drug utilization data indicated appropriate prescribing of patented ESAs consistent with their intended use as a treatment alternative to red blood cell transfusion for anemia associated with myelosuppressive chemotherapy.

The FDA conducted its own evaluation of the impact of multiple actions, including the ESA REMS, on ESA utilization using sponsor-submitted data from outpatient oncology practices between 2006 and 2014 [14]. During 2004–2009, FDA took multiple regulatory actions, including labeling changes. In 2007, the Centers for Medicare & Medicaid Services (CMS) made a National Coverage Determination (NCD) to limit coverage of ESAs for nonrenal disease indications. These actions were followed by a decrease in the proportion of patients receiving chemotherapy using ESAs; an increase in the proportion of patients receiving chemotherapy who initiate ESAs at a hemoglobin level < 10 g/dL; and an increase in the proportion of patients who initiate ESAs at a dosage consistent with product prescribing information. According to the FDA's analysis, full implementation of the ESA REMS in 2011 had minimal impact on trends in these ESA utilization metrics beyond changes observed after a 2008 CMS NCD determination and other FDA regulatory actions. This information led the FDA to conclude that it was no longer necessary to require certification of prescribers and hospitals that prescribe and/or dispense ESAs to patients with cancer to ensure the benefits outweigh the risks. Although the REMS is felt by the FDA to no longer be required to ensure benefits outweigh risks, risks of shortened overall survival and/or increased risk of tumor progression or recurrence associated with ESAs remain. Prescribing information notes increased risk of tumor progression or recurrence, death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access with erythropoiesis-stimulating agents.

Extrapolation Across Clinical Indications

Biosimilar epoetin sponsor received regulatory approval for marketing in all indications for which reference epoetin is licensed. These included anemia treatment for patients with CKD, including patients not on dialysis or who are receiving dialysis; for treatment of anemia due to zidovudine; for treatment of chemotherapy-induced anemia among persons with nonmyeloid malignancies; and to reduce need for allogeneic red blood cell transfusions among patients who are at high risk for perioperative blood loss from elective noncardiac, nonvascular surgery. In 2017, FDA reviewers indicated that the mechanism of action of epoetin is the same as for endogenous EPO; the biosimilar epoetin is highly similar to reference epoetin; PK/PD was similar in healthy subjects; similar efficacy between the two products was demonstrated in animals; the frequency of antidrug antibodies with the proposed biosimilar was low in the clinical studies program evaluating healthy subjects and patients with CKD; and similar clinical safety and clinical efficacy was demonstrated between the two products among patients with CKD on hemodialysis. Although biosimilarity was tested clinically only in the CKD population, FDA reviewers reported in 2017 that clinical evidence supported the sponsor's request for extrapolation for use in other currently approved indications for reference epoetin alfa.

In May 2017, ODAC advisors voted 14 to 1 in favor of recommending the sponsor's biosimilar epoetin application for FDA approval of five dosages that corresponded to FDA-approved dosages of reference epoetin alfa for subcutaneous administration. ODAC reviewers were supportive of analytical comparability findings for both products and that no detectable clinically meaningful differences existed. One panelist stated that data surrounding immunogenicity should not be extrapolated to support approval to zidovudine-associated anemia among HIV-infected individuals.

Patents and Litigation

Amgen's primary U.S. patent for epoetin expired in 2015. In a completed case in federal court, Amgen claimed that the FDA-approved biosimilar epoetin alfa product infringed on two patents while conducting licensing clinical trials (U.S. Patent Nos. 5,856,298 and 5,756,349), one of which covers several EPO isoforms and their selection processes, whereas the other protects proprietary cell lines to manufacture epoetin. The jury awarded $70 million in favor of Amgen. Hospira's appeal was denied.

Naming and Labeling

Naming and labeling conventions are important because biosimilars and reference biologics do not have identical chemical characteristics. FDA finalized its Labeling and Naming Guidance in 2016 [15, 16]. Product-specific suffixes are recommended as the best way to track specific biologics or biosimilars through the entire supply chain, to facilitate pharmacovigilance [13]. The Naming Guidance attaches random four-letter suffixes for reference and biosimilar epoetin and includes the same epoetin base name. The FDA-approved biosimilar epoetin is named "Retacrit" commercially. The product is chemically named "epoetin alfa-epbx."

Interchangeability

The 2019 FDA Biosimilar Interchangeability Guidance outlines regulatory criteria for determining biosimilar interchangeable designations [17]. The sponsor of epoetin biosimilar did not request designation as an interchangeable product, as this is a higher-order regulatory request and requirements for receiving this designation had not

been finalized when FDA approval for biosimilar epoetin was granted in 2018.

Substitution

Forty-five states and Puerto Rico passed legislation preventing automatic substitution irrespective of biosimilars being deemed interchangeable [18]. In all states, the specific name of the epoetin product must be recorded. In some states, the prescribing physician must be contacted, and the recipient patient must be contacted or notified before epoetin substitution occurs. No clear path forward on biosimilar substitution at that state level has been developed. At a minimum, automatic substitution can occur in some states as long as biosimilar epoetin has been approved by the FDA as interchangeable with reference epoetin (which has not occurred).

Pharmacovigilance and Immunogenicity

Two areas of continuing safety concern are antidrug antibody development that has occurred among two patients with chronic kidney disease in a clinical trial who received epoetin biosimilar in Europe and whether long-term pharmacovigilance studies are needed. Unlike European Union requirements, no postmarketing pharmacovigilance plan is required in the U.S. Advisors to the 2017 Oncology Drug Advisory Committee felt that routine pharmacovigilance, supported by unique product names, and absence of occurrence of substitution would facilitate early identification of neutralizing antibodies, particularly in the cancer and HIV setting.

European Union Oncology Experiences with Biosimilar Epoetin

In the European Union, regulatory approval was granted for five biosimilar epoetin brands between 2007 and 2008 (representing two different formulations). The two epoetin biosimilars differ in degree of glycosylation, which affects pharmacokinetics, pharmacodynamics, effectiveness, safety, and immunogenicity. Approvals were based on a totality of evidence concept. Multidose and single-dose vials are approved in Europe (vs. single-dose vials in the U.S.). Most European Union approvals were based on demonstration of comparability with the Eprex formulation of epoetin as the reference product, a formulation marketed in countries outside the U.S. For three biosimilar epoetin brands representing one formulation, extrapolation was granted for all clinical indications approved for reference epoetin alfa in the U.S. and European Union. Two biosimilar epoetin brands in European Union countries (representing one epoetin alfa biosimilar formulation) do not have regulatory authority for allogeneic red blood cell transfusions in the elective noncardiac, nonvascular surgery setting. In the European Union, approval of HX575, the epoetin biosimilar most similar to the epoetin biosimilar approved by the FDA in 2018, is restricted to intravenous administration only, based on phase III studies in 479 patients with chronic kidney disease and 114 patients with cancer [19–21].

Usage of biosimilar epoetin varies by European country, related to regional differences in payment systems [22]. In 2011, 4 years after the first EU biosimilar epoetin launch, the use of biosimilar epoetins was greater than that of first- and second-generation reference epoetin in Sweden and Germany, but uptake in Italy, France, and the U.K. stagnated [23]. Price discounting is limited in some countries. Slow uptake of biosimilar epoetin may reflect efficacy and safety concerns by physicians and patients, including concerns related to immunogenicity (PRCA), hypersensitivity, venous thromboembolism, cardiovascular toxicity, tumor progression, and cancer promotion. However, no unusual or unexpected effects have been reported with European Union biosimilar epoetins [24].

European Union biosimilar epoetin use tracks historical generic drug use in individual countries. Biosimilar epoetin discounts range from 20% to 35% of the price of the reference product. Greece, Finland, and Germany are the largest users of biosimilar epoetins and adopted these products earlier than other European countries [2]. German insurance funds have biosimilar epoetin prescribing targets, because pricing for reference biologicals is high [2]. German physicians view biosimilar epoetin favorably, but physicians in other EU countries are less supportive. In some countries—for example, Finland and France—hospitals have financial incentives to adopt biosimilar epoetin, because hospitals pay for in-hospital drugs but not outpatient ones, which are financed separately [2]. Germany established reference pricing and specific regional targets or quotas for physicians and sickness funds for biosimilar epoetin.

Available European data on biosimilar epoetin have not identified unexpected adverse events [25]. However, for HX575 (the biosimilar epoetin formulation approved in the U.S.), one confirmed case and one suspected case of PRCA developed in two patients with chronic kidney disease receiving subcutaneous HX575 during a clinical trial [26]. The manufacturer determined that tungsten species in the syringes may have caused HX575 protein to unfold, with subsequent aggregates formation [27]. Tungsten appeared to originate from tungsten pins used to form barrels of glass syringes with the final product. HX575 in Europe is now only available for intravenous administration, whereas biosimilar epoetin zeta is approved for intravenous or subcutaneous administration. Observational studies have not identified PRCA or other adverse events with biosimilar epoetin.

Guideline Statements on Biosimilar Epoetin Use in the Oncology Setting in Europe and the U.S.

Biosimilar epoetin prescribing is addressed in the most recent European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) guidelines [28, 29]. The 2019 ESMO guidelines warn against switching from any one erythropoiesis-stimulating agent to another agent (including a biosimilar epoetin) if the patient with cancer and chemotherapy-induced anemia has a stable hemoglobin. Switching is discouraged because of the potential induction of neutralizing antibodies as well as difficulties in assigning toxicity to a specific erythropoiesis-stimulating agent. Automatic substitution is supported only if the patient is erythropoiesis-stimulating agent naïve and the clinician accepts the concept of equivalence. ESMO does not address the formal concept of interchangeability as European

regulatory agencies have not addressed this designation [26]. The 2019 ASCO/ASH Guideline's recommendation 5 indicates that the panel considered all erythropoiesis-stimulating agents to be equivalent based on informal consensus but judging that evidence was of intermediate quality (meaning that the panel had moderate confidence that the available evidence reflects the true magnitude and direction of the net effect) [29]. Only one randomized controlled trial enrolling 60 patients with cancer was available at the time when the panel made recommendations. Therefore, the panel issued a moderate strength of recommendation (meaning that the panel judged that there is moderate confidence that the recommendation reflects best practice) [29]. Unlike ESMO, the ASCO/ASH guideline does not address automatic substitution among patients with cancer with chemotherapy-induced anemia who had initially been treated with a nonbiosimilar erythropoiesis-stimulating agent. However, state pharmacy boards do not permit automatic substitution with biosimilar epoetin if the drug has not been designated by the FDA as interchangeable. To date, no FDA-approved biosimilar has been designated as interchangeable by the FDA.

U.S. Oncology Experience with Biosimilar Epoetin

At launch in 2018, the announced average wholesale price for biosimilar epoetin was listed at 57% less than that of its competitor Procrit. However, rebates are not publicly announced. Nonetheless, in 2019, UnitedHealthcare revised its community and commercial plans' coverage of ESAs [30]. Effective in 2020, patients who were receiving reference epoetin alfa were required to switch to the epoetin biosimilar. Patients who wanted to remain on reference epoetin alfa needed to have their physicians document medical necessity criteria; reference epoetin is considered medically necessary if a patient had minimal clinical response to biosimilar epoetin and a physician attests that a superior response would be expected from reference epoetin or if the patient has a history of intolerance to, contraindication to, or failure of biosimilar epoetin that a physician attests would not be expected with reference epoetin. The revision came after the payer made a prior decision to prefer biosimilar to reference oncology drugs. This included biosimilar bevacizumab, biosimilar trastuzumab, and biosimilar filgrastim. Similarly, AETNA Medicare Advantage and Humana in 2020 designated biosimilar epoetin over reference epoetin in its preferred formulary list [30, 31]. Consistent with these policy changes, usage of biosimilar epoetin increased significantly from 2018 to 2019 and again from 2019 to 2020. In particular, proprietary data obtained from one Medicare insurer indicated that in the setting of epoetin administration for cancer and chemotherapy-induced anemia, use of biosimilar epoetin increased from 0.4% in 2018 to 45.3% in 2019 and 82.1% in 2020, whereas for the related commercial insurer, biosimilar epoetin increased from 1.6% to 17.1% to 62.5% in 2020 (John Brusk, June 12, 2020, personal communication). These numbers are not nationally representative but rather represent biosimilar epoetin reimbursement by one large insurer in the oncology setting. In the Department of Veterans Administration, regional contracts identify preferred sources of epoetin. In at least two large Veterans Integrated Service Networks, regional contracts identify reference epoetin as preferred over biosimilar epoetin, based primarily on VA pricing (Josh Riente, Pharm.D., August 1, 2020, personal communication). Overall, the increase of biosimilar epoetin use in one private health insurer's utilization database reflects the preferred status of biosimilar epoetin in the policy manual for one large national private health insurer. There appears to be a paradigm shift for some oncologists who are beginning to accept oncology biosimilars as agents with similar efficacy and safety as reference oncology drugs. A similar increased uptake has been noted at a county hospital in Oakland, California (Kevin Knopf, M.D., July 2020, personal communication). It should be noted that in some clinical settings, automatic substitution with biosimilar epoetin is occurring despite the absence of FDA designating that biosimilar epoetin is interchangeable with reference epoetin alfa.

Comparison of the First 2 Years of Marketing of Supportive Care Oncology Biosimilars Filgrastim and Epoetin

Recent data have described a similarly fast uptake of biosimilar filgrastim since its initial market approval in 2016 [32]. Overall acceptance was brisk, with the product achieving 50% market share by 2017. Factors that facilitated adoption included designation of large health insurers of biosimilar filgrastim as the preferred filgrastim; acceptance by oncologists of biosimilar filgrastim as having similar safety and efficacy as reference filgrastim; the settling of patent litigation between the manufacturers of reference and biosimilar filgrastim; and pricing that, after rebates, was lower for biosimilar versus reference filgrastim [30]. The adoption of these facilitative efforts in some settings accounted for 60%–80% market share of biosimilar versus reference epoetin and preferred status of biosimilar epoetin by some larger health insurers and at Highland Hospital, a county hospital in Oakland, California. The success of biosimilar epoetin argues favorably for successful rollouts of recently approved therapeutic oncology biosimilars trastuzumab, bevacizumab, and rituximab and for the recently approved formulations of the supportive care oncology biosimilar peg-filgrastim.

Conclusion

The first biosimilar epoetin received FDA approval for marketing in 2018, following two unsuccessful applications in 2015 and 2017. As with many approved biosimilars in the U.S., patent litigation was ongoing even after FDA approval and commercial availability was delayed. After patent litigation was resolved, barriers to biosimilar epoetin existed but had been addressed in ways that mirror the prior efforts with biosimilar filgrastim (Table 2). Pricing was the most important factor that influenced usage. In some settings, price discounts appear to be small and usage of epoetin biosimilar is limited, whereas in many settings, price discounts appeared to be larger. Of note, no other biosimilar epoetin formulations are under FDA review and none are in development; hence, pricing competition going forward will

Table 2. Policy and practical recommendations for improving biosimilar epoetin uptake in the U.S.

Physician-level stakeholder educational efforts, including Continuing Medical Education courses that include information on naming, labeling, extrapolation, substitution, switching, costs, safety, and effectiveness (FDA, manufacturers, and oncology/hematology societies)
Patient- and caregiver-level stakeholder educational efforts including FDA-supported public service announcements (FDA, manufacturers, social media, and oncology/hematology societies)
Pharmacist-level stakeholder educational efforts, including Continuing Pharmacist Education courses (FDA, manufacturers, medical societies, Hematology-Oncology Pharmacy Association)
Payer-level stakeholder educational efforts (FDA, manufacturers, medical societies, and Hematology-Oncology Pharmacy Association)
Ensure that reference epoetin manufacturers allow access to samples to facilitate development of new biosimilar epoetin products via clinical evaluation (FDA)
Improved hospital, payer, pharmacy benefit manager pricing (Private and public insurers)
Make biosimilar epoetin eligible for pass-through payment status (CMS)
Transparent pricing that diminishes the ''rebate trap'' and to ensure that rebates focus on patient access and out-of-pocket costs, not list price (CMS)
Educate physicians and pharmacists on biosimilar switching (FDA)
Decrease use of inter partes reviews and patent infringement lawsuits that prevent entry of new biosimilar epoetins on the market (Federal Trade Commission can control this)
Establish processes to support competitive pricing targeting 25%–30% discounts (CMS and other insurers)
Establish postmarketing safety and real-world data registries (FDA and pharmaceutical manufacturers)
Add a column to the Purple Book for biosimilar epoetin where reference epoetin is also listed along with the date of exclusivity expiration and to provide references to source materials for each regulatory-approved biosimilar epoetin product (FDA)
Allow patients to share in biosimilar cost savings, through reduced out-of-pocket cost requirements (CMS, private health insurers)

Abbreviations: CMS, Centers for Medicare & Medicaid Services; FDA, Food and Drug Administration.

probably be limited. Given licensing and litigation challenges that have been overcome, U.S. marketing now focuses on pricing competition and improving the ease of substitution by pharmacists. Lower prices facilitated policy adoption by at least two large national health insurers and capturing the majority of the epoetin market for cancer for one large health insurer. Experience from the EU, where national and regional health insurance programs have negotiated substantial discounts, suggest that meaningful price discounts will facilitate continued increases in use of the epoetin biosimilar in the U.S. The experience to date in the U.S. has been similarly most promising as that that occurred with biosimilar filgrastim. Going forward, provider and patient confusion over when automatic substitution can occur and whether biosimilar epoetin is interchangeable with other erythropoiesis-stimulating agents persists in the most recent ASCO/ASH clinical guidelines and clinical practice settings.

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Author Contributions

Conception/design: Charles L. Bennett, Shamia Hoque, Martin W. Schoen, Stefano Luminari, Y. Tony Yang, James O. Armitage, Oliver A. Sartor
Provision of study material or patients: Charles L. Bennett
Collection and/or assembly of data: Charles L. Bennett
Manuscript writing: Charles L. Bennett, Sumimasa Nagai, Andrew C. Bennett, Shamia Hoque, Chadi Nabhan, Martin W. Schoen, William J. Hrushesky, Stefano Luminari, Paul Ray, Paul R. Yarnold, Bart Witherspoon, Josh Riente, Laura Bobolts, John Brusk, Rebecca Tombleson, Kevin Knopf, Marc Fishman, Y. Tony Yang, Kenneth R. Carson, Benjamin Djulbegovic, John Restaino, James O. Armitage, Oliver A. Sartor
Final approval of manuscript: Charles L. Bennett, Sumimasa Nagai, Andrew C. Bennett, Shamia Hoque, Chadi Nabhan, Martin W. Schoen, William J. Hrushesky, Stefano Luminari, Paul Ray, Paul R. Yarnold, Bart Witherspoon, Josh Riente, Laura Bobolts, John Brusk, Rebecca Tombleson, Kevin Knopf, Marc Fishman, Y. Tony Yang, Kenneth R. Carson, Benjamin Djulbegovic, John Restaino, James O. Armitage, Oliver A. Sartor

Disclosures

Charles L. Bennett: Oncology Analytics (C/A); **Sumimasa Nagai:** Astellas, Bayer, Sawai Pharmaceutical, TakaraBio (H); **Chadi Nabhan:** Caris Life Sciences (E); **Stefano Luminari:** Roche, Celgene/Bristol-Myers Squibb, Takeda, Janssen (SAB); **Laura Bobolts:** Oncology Analytics (E); **John Brusk:** Oncology Analytics (E); **Rebecca Tombleson:** Oncology Analytics (E); **Marc Fishman:** Oncology Analytics (E); **James O. Armitage:** Contatus IDMC, Samus Therapeutics, Ascentage Board of Directors, Tesaro Bio, Inc. (C/A); **Oliver A. Sartor:** Advanced Accelerator Applications, Astellas, AstraZeneca, Bavarian-Nordic, Bayer, Bellicum, Blue Earth Diagnostics Inc., Celgene, Constellation, Dendreon, EMD Serono, Endocyte, Johnson & Johnson, Myovant, Pfizer, Progenics, Sanofi, Teva (C/A), AstraZeneca, Bayer, Bristol-Myers Squibb, Constellation, Dendreon, Endocyte, Innocrin, Invitae, Johnson & Johnson, Merck, Progenics, Roche, Sanofi, SOTIO (RF), Johnson & Johnson (H), Noria Therapeutics (OI), Sanofi (ET). The other authors indicated no financial relationships.

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