Biosimilars and their use in hematology and oncology

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The patent expiration of several biopharmaceuticals such as erythropoietin (erythropoiesis-stimulating agents, ESAs), granulocyte colony-stimulating factor (G-CSF, filgrastim) and others, has led to the emergence of biosimilar medicines. These are defined as copy versions of approved medicinal products with demonstrated similarity in physicochemical characteristics, efficacy, and safety based on a comprehensive comparability exercise. Strict guidelines for the development of biosimilars, ranging from preclinical to phase III trials and postmarketing studies, are already in place in Europe, and the United States Food and Drug Administration (FDA) recently issued draft guidance on biosimilars. A number of biosimilar ESAs and G-CSFs have been approved. Biosimilar monoclonal antibodies are an attractive target for development, with draft guidance from the European Medicines Agency currently under review. Biosimilar medicines may provide cost-effective alternatives to their branded counterparts, potentially benefitting public health by improving access to these medications. It is therefore important to raise awareness of these products among treating physicians. Furthermore, finalization of FDA guidance is important for the development of biosimilar medicines for the US market.

Biologic medicines developed through recombinant DNA technology, such as insulin, growth hormone and cytokines (eg, erythropoietin and hematopoietic growth factors), have revolutionized the treatment of many disorders, such as anemia, diabetes, and cancer. These biologic medicines are larger, more complex, and more heterogeneous than are traditional small-molecule chemical medicines.[1,2] Biologic medicines are typically produced within specially engineered cells and their properties often depend on the nature of the manufacturing process; differences in manufacturing processes, protein source, and extraction and purification methods can lead to heterogeneity of the resulting products as well as to difficulties in their characterization[1] (Figure 1[3]).

The patent expiration on early biologic medicines has allowed for the development of biosimilar medicines across the world.[1] In the European Union (EU), the Biosimilar Medicinal Products Working Party emphasizes the importance of correctly defining biosimilars.[4] According to the EU guidelines, a biosimilar medicinal product is a copy version of an authorized biologic medicine, known as the reference product, which has demonstrated similarity, through a comprehensive comparability exercise, to the reference product in terms of physicochemical characteristics, efficacy, and safety. Only products that have been subjected to this rigorous development process can be defined as biosimilars. However, various terms have emerged in different parts of the world for copy versions of original biologic medicines, which have not been subjected to the same rigorous comparability testing required in the EU and other highly regulated non-EU markets.[4,5] Analysis of copy epoetin products that were marketed outside of the United States and EU demonstrated that the composition of copy versions of biologic medicines varied widely from the originator products.[6] The imprecise terminology in these circumstances can give rise to negative perception and impaired acceptance of biosimilars among prescribing physicians and patients, highlighting the need for both standardized terminology and rigorous approval processes for biosimilars and other copy versions of original biologic medicines.

The biosimilars regulatory pathway

EU guidelines

The European Medicines Agency (EMA) introduced guidelines for the development and approval of biosimilars in 2005.[7] These guidelines

Manuscript received May 4, 2012; accepted May 5, 2012.

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Disclosures: The author has a consultancy agreement with Hospira UK Ltd.

Commun Oncol 2012;9:198-205
http://dx.doi.org/10.1016/j.cmonc.2012.05.004

state that comparability with an original biologic reference product must be ensured through extensive testing at all stages of development, including quality, nonclinical, and clinical evaluation.[7] The biosimilar must show no clinically significant differences to the reference product in quality, efficacy, and safety.[7] If clinical similarity is proven for one indication, then the EMA has endorsed the concept of data extrapolation to other indications as long as the mode of action is the same in those indications.[7] Postapproval pharmacovigilance and monitoring of immunogenicity are also required based on the known safety profile of the reference product. Specific guidelines have also been issued for the development of biosimilar erythropoiesis-stimulating agents (ESAs),[8] myeloid growth factors,[9] and somatropins,[10] which has led to the approval of a number of products within the EU (see Table 1).[1] The EMA is also finalizing its guidance on biosimilar products that contain monoclonal antibodies (mAbs).[11]

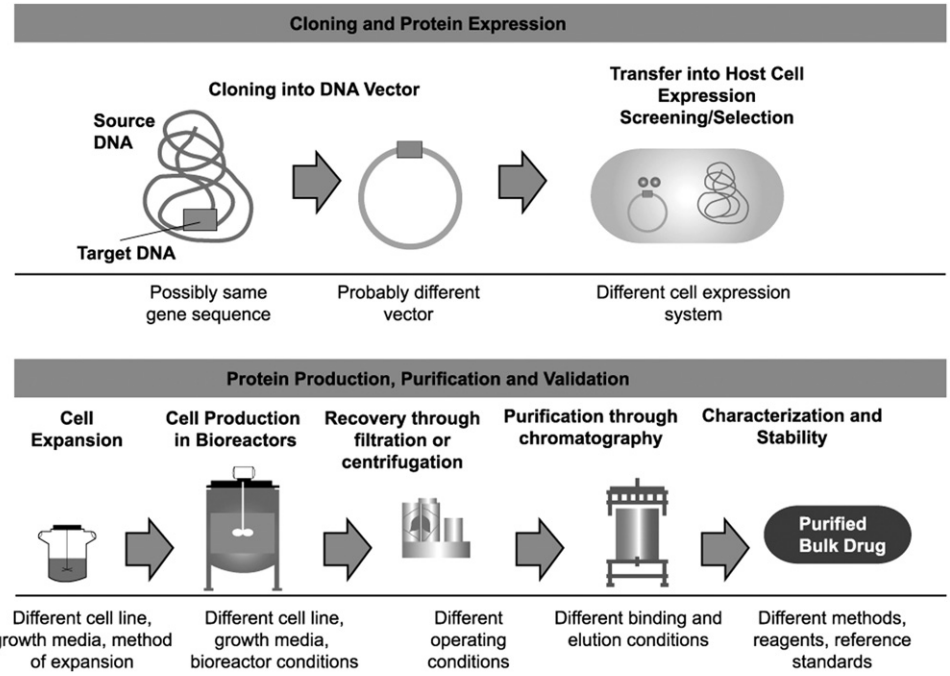

FIGURE 1 Recombinant protein production: sources of variation between manufacturers.[3]
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World Health Organization guidelines

Guidelines from the WHO for the development and approval of biosimilars are similar to EMA guidance on establishing biosimilarity.[12] These guidelines could be particularly important for countries without a rigorous approval process for biosimilars as well as for use in less strictly regulated markets, such as China and India, where copy versions of biologic medicines are already available.

US guidelines

Guidance for biosimilar medicines in the United States is currently lagging behind the EU. However, the Biologics Price Competition and Innovation (BPCI) Act, part of the US Affordable Care Act, was enacted in March 2010 to promote competition in the biologic market. The BPCI Act outlines an abbreviated licensure pathway for biologic products that have been shown to be biosimilar to, or interchangeable with, an FDA-approved biological reference product. The enactment has also led the FDA to issue draft guidelines to assist in the development and approval of biosimilar medicines in the United States.[13] The draft guidance states that submission of a licensing application for a biosimilar through the abbreviated pathway must demonstrate biosimilarity to a reference product based on data derived from analytical studies, animal studies, and a clinical study or studies. In addition, for a biosimilar to be considered interchangeable—that is, enabling a pharmacist to substitute a biosimilar with the originator drug without the intervention of the original prescribing physician—evidence must be provided that the biosimilar produces the same clinical result as the reference product in any given patient, and the safety and efficacy of switching between the biosimilar and reference product must be demonstrated.[13]

The BPCI Act gives the FDA the authority to make assessments as to how much preclinical and clinical data will be required for approval of biosimilars. The agency plans to use a "totality of the evidence" approach, evaluating all available data submitted in support of the biosimilarity of the proposed product, and the analyses and testing required to ensure safety, purity, or potency will be determined on a product-specific basis. Given these requirements and the fact that manufacturers will be required to disclose potentially sensitive information on the production and development process of the biosimilar, it is possible that manufacturers may opt out of the abbreviated pathway for approval. However, the guidance encourages discussion with manufacturers at all stages of biosimilar development.[13]

TABLE 1 Biosimilar products available in the EU[1]

Reference product	Marketing authorization holder	EU approval, y	Brand name
Somatropin	Sandoz GmbH	2006	Omnitrope
	Biopartners GmbH	2006	Valtropin
Epoetin alfa	Sandoz GmbH	2007	Binocrit
	Hexal GmbH	2007	Epoetin alfa HEXAL
	Medice Arzneimittel	2007	Abseamed
Epoetin zeta	Hospira UK	2007	Retacrit
	STADA Arzneimittel GmbH	2007	Silapo
Filgrastim	Ratiopharm GmbH	2008	Ratiograstim
	Teva Generics GmbH	2008	TevaGrastim
	CT Arzneimittel GmbH	2008	Biograstim
	Sandoz GmbH	2008	Zarzio
	Hexal GmbH	2009	Filgrastim HEXAL
	Hospira UK	2010	Nivestim

Biosimilars in hematology and oncology

The introduction of biologic medicines into the treatment of hematologic and oncologic diseases has improved clinical outcomes (including overall survival), and they are now an essential feature of the many clinical guidelines for cancer management.[14-16] Biologic medicines, such as granulocyte colony-stimulating factor (G-CSF) and ESAs are also vital in the treatment of chemotherapy-induced neutropenia and anemia, respectively, according to supportive care guidelines.[14-16] Following the patent expiration of many of these products in the EU, biosimilar versions have now been approved (see Table 1).

Biosimilar G-CSF

The hematopoietic growth factors (HGFs) are a family of glycoproteins that play an important role in the regulation of hematopoiesis, the process of generating blood cells.[17] G-CSF, a naturally occurring HGF produced by endothelial cells, macrophages, and other immune cells, stimulates the proliferation and differentiation of hematopoietic stem and progenitor cells committed to neutrophil lineages as well as activating fully differentiated neutrophilic granulocytes.[18-20] Neutropenia, a decrease in circulating neutrophils, is a serious and relatively common complication of myelosuppressive chemotherapy.[21] Furthermore febrile neutropenia (FN), a major risk factor for morbidity and mortality,[22] is associated with dose delays and/or reductions in potentially curative treatment regimens for tumors such as lymphoma and breast cancer.[23] Therefore, the discovery that G-CSF could stimulate the production of neutrophils was an important step in understanding the regulation of hematopoiesis, leading to the molecular cloning of filgrastim.[24-25] Early clinical studies showed that filgrastim produced an immediate transient leukopenia followed by a sustained, dose-dependent increase in circulating neutrophils.[17] Subsequent clinical trials and meta-analyses established that primary prophylaxis with filgrastim (beginning in the first cycle of chemotherapy) reduced the incidence of FN, FN-related hospitalizations, intravenous (IV) anti-infective use, infection-related mortality, and the need for chemotherapy dose modification, compared with placebo or no treatment, in many tumor types.[16] Filgrastim was first approved in 1991 in Europe and the United States, under the trade name Neupogen (Amgen Europe; Breda, The Netherlands)[26] and is a 175-amino acid recombinant protein with a molecular weight of 18.8 KDa. Human native G-CSF is glycosylated, but Neupogen is a nonglycosylated protein, produced in genetically modified *Escherichia coli* (*E.coli*).[24-25] Its amino acid sequence is identical to that of human G-CSF, except for an additional N-terminal methionine.[25-26] In addition, a pegylated recombinant human filgrastim with a longer half-life, pegfilgrastim (Neulasta, Amgen Europe; Breda, The Netherlands), has been developed.[27] Another recombinant human G-CSF, lenograstim (Granocyte, Chugai), is available; this differs from filgrastim as it is manufactured in mammalian Chinese hamster ovary cells and is glycosylated during production.[28]

The risk and adverse sequelae of FN can be reduced through the prophylactic use of G-CSF in at-risk individuals,[15,21] with guidelines in the United States[14-15] and Europe[21] recommending prophylactic G-CSF with chemotherapy regimens associated with FN in more than 20% of patients. The indications for Neupogen are pre-

vention and treatment of neutropenia and of FN in patients undergoing cytotoxic chemotherapy.[26] Other current indications are reduction in the duration of neutropenia in patients who are undergoing myeloablative therapy followed by bone marrow transplantation and who are considered to be at increased risk of prolonged severe neutropenia; mobilization of peripheral blood progenitor cells (PBPC); treatment of severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections; and treatment of persistent neutropenia (ANC $\leq 1.0 \times 10^9$/L) in patients with advanced HIV infection.[26] The expiration of the Neupogen patent in the EU in 2008 has led to the development of three biosimilar filgrastims, with Neupogen as the reference product, marketed under different brand names by different companies (Table 1).

Clinical evaluation of Nivestim (filgrastim). This biosimilar, marketed by Hospira Ltd (Royal Leamington Spa, UK), has been developed with a preclinical and clinical program as recommended by the EMA.[29] The bioequivalence of Nivestim and Neupogen has been demonstrated through physicochemical,[30] pharmacokinetic,[31] pharmacodynamic,[32] and clinical studies.[33] The efficacy and safety of Nivestim compared with Neupogen for the prevention of neutropenia in patients receiving myelosuppressive chemotherapy for breast cancer was studied in a phase III randomized, double-blind, therapeutic equivalence study.[33] The study was conducted in women with invasive breast cancer suitable for docetaxel and doxorubicin combination chemotherapy (a treatment associated with a high risk of developing FN). In all, 279 patients were treated with Nivestim or Neupogen (5 μg/kg by subcutaneous [SC] injection for both treatments), administered at least 24 hours after chemotherapy, and continued once daily until the documented ANC nadir had passed and ANC was greater than 3×10^9/L, or for 14 days, whichever occurred first. The primary objective of the study was to test the therapeutic equivalence of Nivestim and Neupogen, using the primary end point of duration of severe neutropenia (DSN) in days (ANC $< 0.5 \times 10^9$/L) during the first chemotherapy cycle. The secondary efficacy end points included DSN in cycles 2 and 3, time to ANC recovery (ANC $> 3 \times 10^9$/L), and incidence of FN (ANC $< 0.5 \times 10^9$/L; body temperature, $\geq$ 38.5°C) in cycles 1 to 3, as well as safety of the treatment. Nivestim- and Neupogen-treated patients had a similar mean DSN (treatment cycle 1: Nivestim: 1.6 days, Neupogen: 1.3 days). The 95% confidence interval for difference in the adjusted mean DSN in treatment cycle 1 was within the predefined range (−1 to +1 day) required to demonstrate bioequivalence; therefore the primary end point was met. Furthermore, the mean ANC in treatment cycle 1 was similar in the Nivestim- and Neupogen-treated patients (Figure 2), and the mean time to ANC recovery in treatment cycle 1 was the same in both groups. The frequency of hospitalization because of FN was also the same between the Nivestim and Neupogen treatment groups.[33]

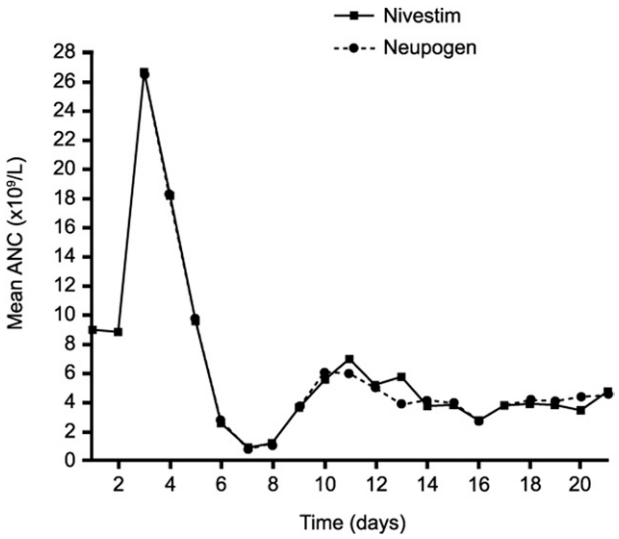

FIGURE 2 Mean ANC (x 10^9/L) over time in cycle 1 (per protocol population).[33] ANC indicates absolute neutrophil count.

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A similar percentage of patients in each of the treatment groups experienced adverse events (AEs; 86.9% and 84.2%, in the Nivestim and Neupogen groups, respectively) and the incidence of grade 3 or 4 treatment-emergent AEs was almost identical, Nivestim (12.57%) and Neupogen (12.63%). In both of the treatment groups, the most frequent treatment-related AEs were nausea, fatigue, and bone pain. No neutralizing antibodies to filgrastim were recorded in any patient. Furthermore, no notable changes in laboratory parameters were observed for any patient. This led to the approval of Nivestim by the EMA in June 2010 for all indications of the originator product Neupogen. EMA guidelines support the extrapolation of clinical data from one therapeutic indication to another, assuming that reasonable justification can be made following consideration of clinical experience, current literature, similarity of the mechanisms of action and any possible safety issues in different patient subpopulations.

Biosimilar erythropoiesis-stimulating agents

Anemia is common in patients with cancer who are undergoing chemotherapy, with about 50% of patients de-

veloping chemotherapy-induced anemia (CIA).[34] Anemia can impair the patient's functional status, diminish physiologic reserve, and cause fatigue that can be disabling.[35] Anemia treatment includes red blood cell (RBC) transfusions and in case of iron deficiency, iron supplementation.[21,36,37] RBC transfusions have the benefit of quickly increasing hemoglobin (Hb) levels; however they are associated with risks, such as transmission of infectious pathogens and transfusion-related acute-lung injury.[38] Therefore, ESAs were developed with the aim of reducing transfusion dependence. ESAs increase RBC production in bone marrow by activating the erythropoietin receptor (EpoR) on erythrocytic progenitor cells.[39,40] Endogenous erythropoietin (EPO) consists of a central polypeptide core covered by posttranslationally linked carbohydrates. The molecular cloning of recombinant human EPO (rHuEPO) resulted in the introduction of epoetin alfa, in 1989.[41] First-generation ESAs typically have a relatively short half-life and have traditionally been administered up to 3 times per week IV or SC to maintain adequate Hb levels.[41] Darbepoetin alfa (Aranesp, Amgen Europe; Breda, The Netherlands[42]), a second-generation hyperglycosylated ESA was subsequently introduced with a longer half-life than epoetin alfa, owing to two additional N-linked carbohydrate chains attached to the protein.[43] More recently, a third-generation ESA, Continuous Erythropoiesis Receptor Activator (CERA; Mircera, Roche[44]), which has an integrated methoxy-polyethylene glycol polymer chain and a longer half-life than first- and second-generation ESAs.[45]

After the patent expiration of the originator epoetin products in Europe, a number of biosimilar epoetins have been developed. Two biosimilar epoetins (substance HX575, epoetin alfa and substance SB309, epoetin zeta), marketed under five separate names, have been approved by the EMA (Table 1). These have been developed with a thorough preclinical and clinical program according to EMA guidelines and have both used Eprex/Erypo as the reference product.

Clinical evaluation of Retacrit (epoetin zeta). This biosimilar ESA (Hospira Ltd, Royal Leamington Spa, UK), is indicated for the treatment of patients with renal anemia and for patients with symptomatic CIA.[46] The current EU regulatory procedure for biosimilar ESAs, overseen by the EMA, requires comparative efficacy of the biosimilar ESA compared with the reference product to be demonstrated in the setting of renal anemia.[8] Therefore, phase III studies were conducted demonstrating that Retacrit is therapeutically equivalent to epoetin alfa (Eprex, Janssen-Cilag Ltd, High Wycombe, UK) for correction and maintenance of Hb levels when given either IV or SC in patients with anemia and end-stage renal failure on chronic hemodialysis.[47-50] In a longer-term study, Retacrit (IV) effectively maintained target Hb levels for up to 108 weeks, with good overall long-term tolerability in patients with anemia and end-stage renal failure on chronic hemodialysis.[47] In these studies, Retacrit was associated with a similar number and severity of AEs as epoetin alfa when administered IV or SC to patients with renal anemia.[47-50]

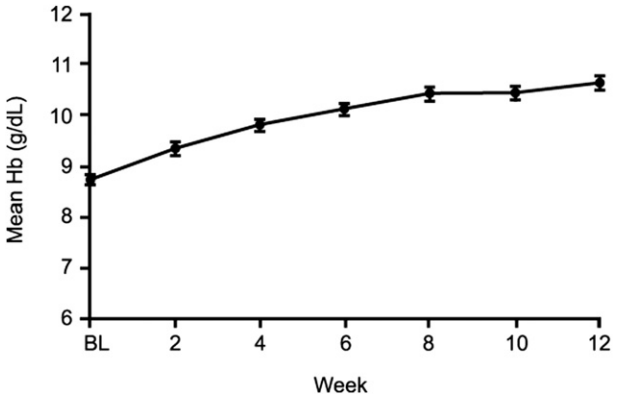

FIGURE 3 Mean (standard error of mean) Hb levels from baseline to week 12 in 216 patients with chemotherapy-induced anemia who received epoetin zeta. Missing data were input using last observation carried forward.[51]

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Although comparative studies in CIA are not required for biosimilar ESAs, the effectiveness and safety of Retacrit in CIA was demonstrated in an open-label, international, 12-week, multiple-dose, phase III study in 216 patients receiving chemotherapy and who had anemia (Hb $<$ 10 g/dL) and were at risk of transfusion.[51] In that study, Retacrit steadily improved Hb levels, with a mean Hb increase of 1.8 g/dL from baseline over 12 weeks (Figure 3). Furthermore, 71% of patients (153/216) who received Retacrit achieved an Hb response of $\geq$ 2.0 g/dL or reticulocyte increase of $\geq$ 40,000 cells/μL within 8 weeks of therapy initiation, and 81% of patients receiving Retacrit did not require blood transfusions by week 12. Clinically significant thromboembolic events occurred in 4.2% of patients, which is within reported rates in studies with other ESAs (median, 4.5%; range, 0%-30%).[52] In addition, all quality-of-life ratings (energy levels, ability to do daily activities, overall quality of life) showed continuous improvements during Retacrit treatment.[51]

Health economic benefits of biosimilars

Although biological medicines have brought benefits to many patients with chronic or life-threatening diseases, they are often expensive, which means that access to these important treatments can be restricted in many parts of

the world.[1] By contrast, because of the reduced costs associated with the development of biosimilars, they are likely to offer health economic benefits, improve patient access to medication, and provide more treatment options.[1] It has been postulated that if biosimilar medicines were used as alternatives to only seven conventional biopharmaceuticals within the EU, savings of more than €2 billion could be achieved.[1] Indeed, a cost-efficiency study conducted across the European G5 countries (Germany, France, Italy, Spain, and the UK) suggested that treatment with a biosimilar filgrastim product (Zarzio, Sandoz GmbH, Kundl, Austria) was the most cost-efficient approach to reduce the incidence of FN in chemotherapy-treated patients.[53] The cost benefits associated with biosimilar products could account for their increasing market share in Europe [Hospira, data on file].

However, regulatory requirements for biosimilars have a direct effect on product development costs. Although the BPCI Act in the United States was introduced to grant patients access to cheaper versions of prohibitively expensive drugs, some have argued that it will be very difficult for manufacturers to make biologic drugs cheaper if they are subjected to the same standards for proving safety and efficacy as original innovator companies developers. The guidelines for regulatory approval of biosimilar medicines are yet to be finalized in the United States and therefore their impact on the cost of biosimilars in the United States is, as yet, unknown.[54]

Biosimilar monoclonal antibodies

Antibody-based therapies are important components of treatment regimens for many malignancies.[55] Biosimilar monoclonal antibodies (mAbs) are likely to be a significant development in antibody therapeutics in the next few years as some patents of widely prescribed mAbs used in oncology will begin to expire, such as Rituxan/Mabthera (rituximab, Genentech, Grenzach-Wyhlen, Germany), Remicade (infliximab, Janssen-Cilag), Herceptin (trastuzumab, Genentech, Grenzach-Wyhlen, Germany), Humira (adalimumab, Abbott, Berkshire, UK), Avastin (bevacizumab, Genentech, Grenzach-Wyhlen, Germany).[56] However, the relevant legislation for the approval of biosimilar mAbs is still under debate, and there are many challenges that need to be overcome. The EMA's Biosimilar Medicinal Products Working Party has therefore drafted guidelines for biosimilar mAbs.[11]

MAbs are larger structures with a mass of about 150 kDa, which means that comparability exercises for biosimilar monoclonal antibodies could be challenging.[56] Although EU legislation for biosimilar mAbs has yet to be finalized, other less regulated markets have already launched copy biologics of marketed mAbs, such as Reditux (a copy version of rituximab developed by Dr Reddy's Laboratories) approved in India in 2007.[57] However, as mentioned previously, such products cannot be considered true biosimilars, as defined by EU guidelines requiring a product to have extensive comparability data and a rigorous approval process. Nevertheless, the first EU application for a biosimilar mAb has recently been submitted by Celltrion (partnered with Hospira) for a biosimilar version of the autoimmune drug Remicade (infliximab, Janssen-Cilag). Remicade is a mAb against tumor necrosis factor (TNF) alpha licensed in the EU to treat rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.[58]

Summary

Biologic medicines have a critical role in the care of patients with hematologic disorders and solid tumors, with guidelines recommending their use in cancer management and supportive care. As patents for these biologic medicines begin to expire, biosimilars will become an important addition to the range of treatment options available to clinicians. Indeed, in the EU, a number of supportive care products have already been approved. Furthermore, patents on some of the most widely prescribed mAbs used in oncology are due to expire over the coming years, which is likely to lead to the introduction of biosimilar versions of these treatments. The EMA has preempted this development with the issue of draft guidance for the development and approval of biosimilars mAbs. These may also provide cost-effective alternatives to their branded counterparts, potentially benefiting public health by improving access to these medications.

Immunogenicity is an important safety issue concerning all biosimilar products. Postapproval pharmacovigilance and surveillance are therefore crucial for the approval process. In oncology/hematology, biosimilar ESAs have additional postmarketing studies in their risk-management plan to address safety concerns such as pure red cell aplasia, thrombotic vascular events and tumor growth potential. With regards biosimilar G-CSF products, data extrapolation has raised some concerns, particularly with regard to the use for PBPC mobilization and transplantation.[59] Therefore, the European Group for Blood and Bone Marrow Transplantation currently recommends the use of biosimilars in healthy donors only in the context of prospective clinical trials specifically designed to address the efficacy of these compounds in mobilizing progenitor cells into peripheral blood as well as both short- and long-term safety aspects.[60] The resulting data will potentially allow the widespread use of these compounds in this setting. The pharmacovigilance and postmarketing stud-

ies are therefore a crucial part of the biosimilars development program.

As patents in the United States are soon to expire on many biologic products used for the treatment of patients with cancer, it is important for physicians to be informed and understand the application of biosimilars to clinical practice. A recent survey of health-care professionals carried out by the National Comprehensive Cancer Network Work Group, revealed that most of respondents were unfamiliar with recent developments regarding biosimilars (55% of respondents) although interest in biosimilars appeared high.[52] These results highlight the need for raising awareness of the principles of biosimilars. The finalization of the FDA guidance will be an important step in the development of biosimilar medicines for the US market.

Acknowledgments

Editorial assistance was provided by NeonMedical and funded by Hospira UK Ltd.

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