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REVIEW ARTICLE

Worldwide Network for Blood and Marrow Transplantation (WBMT) perspective: the role of biosimilars in hematopoietic cell transplant: current opportunities and challenges in low- and lower-middle income countries

This article has been corrected since Advance Online Publication and a correction is also printed in this issue

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Abstract

Health care costs attributed to biologics have increased exponentially in the recent years, thus biosimilars offer a possible solution to limit costs while maintaining safety and efficacy. Reducing expenditure is vital to health care especially in developing countries where affordability and access to health care is a major challenge. We discuss the opportunities and the challenges of biosimilars in the field of hematopoietic cell transplantation (HCT) in low- and lower-middle income countries. Developing countries can potentially invest in the forecasted costs reduction by utilizing biosimilars. This can be used to decrease the costs of procedures such as HCT, which is a rapidly growing field in many developing regions. The introduction of biosimilars in the developing regions faces many challenges which include, but are not limited to: legal and regulatory issues, lack of research infrastructure, and the presence of educational barriers. Thus, collaborative efforts are needed to ensure an effective and safe introduction of biosimilars into low- and lower-middle income countries.

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Introduction

The therapeutic use of biologics, such as growth factors monoclonal antibodies, has expanded tremendously over the last two decades. Biologic drugs have demonstrated success in treating many diseases in various medical specialties, including endocrinology, rheumatology, and hematology/oncology [1, 2]. However, biologics tend to be more expensive compared with traditional drugs due to the complex manufacturing process, which has contributed to their high costs. For instance, the sales of the top ten biologic drugs comprised ~77 billion US dollars in year 2013 [3]. Thus, efforts are being made to limit this expense using generic drugs and biosimilars following patent expiration. The definition of biosimilars varies across different health care institutions, including World Health Organization (WHO), United States Food and Drug Administration (US-FDA) and the European Medicines Agency (EMA) [1, 4]. However, all definitions agree that "biosimilars" must be chemically similar to their reference biological products with no clinically significant differences [5, 6]. The process of approval of biosimilars usually includes analytical studies (e.g. biologic and chemical characterization) followed by preclinical and clinical validation studies, usually requiring a phase 3 randomized trial of the biosimilar versus the originator product [6].

Medication related expenditures constitute a major component of cost related to oncology and hematology patients, including hematopoietic cell transplant (HCT) recipients [4]. High health care expenditure hinders access to health care worldwide and even more so in low- and lower-middle income countries with restricted resources. It is speculated that biosimilars could potentially decrease cancer health care costs and be a major factor for expanded access in developing countries [7, 8]. The introduction of biosimilars in the field of HCT will require better understanding of their nature and potentials by physicians, health care practitioners, and payers. Here-in, we introduce the concept of biosimilars and their different associated specifics, and discuss opportunities and challenges associated with use of biosimilars for HCT, especially in countries with restricted resources.

Biosimilars, cancers and low- and lower-middle income countries

HCT in low- and lower-middle income countries

Despite the utility of HCT in treating and potentially curing many diseases, it is an expensive modality, particularly allogeneic (allo) HCT [9, 10]. The expansion of indications for HCT in treating hematologic and nonhematologic diseases has necessitated the development of new programs worldwide. Developing a transplant program is challenging, especially in developing countries [11]. This created a gap in HCT activity between developing and developed countries.

Worldwide Network for Blood and Marrow Transplantation (WBMT) reported the data of the one million HCTs that were performed between the years 1957 and2012 [12]. Table 1 compares the number of HCTs performed between the years 1986–1991 and 2006–2012. The table shows that the regions with the highest increase in HCT activity were South East Asian and Western Pacific and Eastern Mediterranean and African, with 20.9- and 31.1-fold increases, respectively. A combined report by East-Mediterranean (EMBMT) and African (AfBMT) Blood and Marrow Transplantation Groups and WBMT noted that only 2% of the active 1570 transplant teams worldwide are in East-Mediterranean (EM) and African regions [13]. The active teams are only present in 12 out of the 68 countries in the two regions, with a reported very low median number of HCT/10 million inhabitants; 32.8 compared with 128.5, worldwide [13]. This is considered low when compared with the European and American regions. However, the rate of increase in HCT number in EM region is higher than the rate of population increase [14, 15]. Latin America, with many developing and emerging economies, has a 20–40 fold lower frequency of HCT, when compared with Europe and North America [16].

Despite the quantitative difference in HCT activity, transplant outcomes in the EM region were comparable to those in the European Bone Marrow Transplant (EBMT)

Table 1 HCT activity worldwide between 1986 and 2012 [12]

Region	Number of HCTs 1986–1991 (%)	Number of HCTs 2006–2012 (%)	Fold increase
Pan-American	14,975 (37.6)	119,140 (28.5)	7.0
South East Asian and Western Pacific	3349 (8.4)	73,342 (17.5)	20.9
Eastern Mediterranean and African	300 (0.75)	9625 (2.3)	31.1
European	21,152 (53.2)	21,5941(51.7)	9.2
Total	39,776	418,048	9.5

society [17]. Bazarbachi et al. [17], showed that the incidence of acute and chronic graft-versus-host-disease (GVHD) were similar in transplant centers of both societies. Moreover, prognostic and mortality indicators including nonrelapse mortality, 3-year leukemia-free survival, and overall survival were similar despite the more limited resources and overall lesser transplant experience in the EM region. These data illustrate the growth of transplant, with substantial future potential.

Starting an HCT program in countries with restricted resources is challenging, due to many different factors, including economic, social, and infrastructural reasons [11]. The costs of establishing tertiary centers that will host HCT programs are huge. Thus a major challenge facing developing countries is to find effective strategies to cut costs. A report by the WBMT, showed that factors related to macroeconomics such as Governmental health care expenditure and Gross national income/capita is strongly correlated with HCT numbers [15].

HCT costs and the burden of pharmaceutical costs

Different cost-analysis studies approximated HCT-related expenses. Costs of allo HCT were higher than autologous HCT [9, 10]. The costs were variable between different countries and regions. In a review [9] of different costs studies (mainly from the US), the 1 year cost after an allo HCT was between 96,000 and 204,000 USD. The contribution of medication costs to the final cost of HCT was sizeable, nearing 40% of the total, with antibiotics and colony-stimulating factors representing the major contributors [9].

There are few HCT cost studies available from developing countries. The costs of HCT in Jordan were ~35,000 USD for an autologous HCT and 66,000 USD for an allo HCT, but the study did not provide a cost distribution analysis [18]. In one Mexican study, the estimated cost of allo HCT over the first year was around 12,500 USD, with medications (both inpatient and outpatient) noted as the most expensive component of the total cost [19]. In one study from Northern India the median cost of allo HCT was 17,914 USD (range 10,832 USD–44,701 USD), out of which 25% were pharmacy-related charges [20]. Cost-analysis studies are not always comparable due to the omission of indirect costs, the salary scale of regional health care workers, and small sample sizes. These studies might not be representatives of the costs in different countries, as they are mainly institutional studies, however they demonstrate the costly nature of HCT and emphasized the major expense from medications to the final costs, both in developing and developed countries.

Biosimilars' utility

Biosimilars applications in hematology/oncology

Availability and use of biologics in hematology and oncology have increased significantly in recent years. They have been used for multiple types of cancer, and contributed to nearly 55% of oncology related outpatient pharmaceutical expenditure in 2010; while 40% of the biotechnology medicines in development are targeting cancers and blood disorders [3, 8]. Thus, the economic impact of biologics in cancer care is vast. The high costs of biologics limit access to cancer care worldwide, particularly in developing countries. In the last decade, the expiration of many biologics' patents facilitated the increase in approved biosimilar cancer treatments in the United States (US) and European Union (EU) [21–23].

Opportunities for biosimilars in HCT

In recent years, the use of biologics has been vital to HCT, particularly using growth factors for apheresis of peripheral blood stem cells (PBSC). To evaluate the trends in biosimilars use and their efficacy and safety issues, we performed a systematic search. Our search methodology involved the following databases: Cochrane Central Register of Controlled Trials and Database of Systematic Reviews and Ovid-MEDLINE. In addition, abstracts from American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT) and EBMT group in the last 5 years were screened. The search strategy utilized Boolean logic to combine terms like: "Bone Marrow Transplantation" and "Hematopoietic Stem Cell Transplantation" with terms like: "Biosimilar" and "Biosimilar pharmaceuticals".

The database search identified 78 manuscripts. Their abstracts were screened, and 28 studies evaluated the efficacy of biosimilars in comparison to the original biologic. The majority of studies were retrospective including a few noninferiority studies. All articles discussed granulocyte colony-stimulating factor (G-CSF) analogs and their role in stem cell mobilization for autologous HCT and for allo donors and posttransplant recovery and engraftment. In the last 5 years, fewer than ten abstracts presented in ASBMT meetings discussed biosimilars. All the presented abstracts were investigating the use of filgrastim biosimilars. More abstracts discussing biosimilars were presented in EBMT annual meeting, including six in the 2018 EBMT meeting.

With increasing numbers of approved biosimilars, additional studies should assess the efficacy and safety of these drugs in HCT and its associated complications. Up-to-date, none of the approved biosimilars has shown any significant concerns regarding either clinical efficacy or safety profile.

Table 2 Biosimilars approved in the United States and the European Union pertaining to HCT

Original biologic	Biosimilars approved[a]	Year of approval (regulatory body)	Approved/ possible uses in HCT
Filgrastim	Tevagrastim	2008 (EMA)	−Mobilization of stem cells for auto-HCT[b] −Mobilization of stem cells in allo-HCT donors −Cell recovery after transplant
	Ratiograstim	2008 (EMA)	
	Filgrastim Hexal	2009 (EMA)	
	Zarzio	2009 (EMA)	
	Accofil	2014 (EMA)	
	Zarxio	2015 (US-FDA)	
	Nivestim	2010(EMA)	
	Grastofil	2013 (EMA)	
	Nivestym	2018 (US-FDA)	
Rituximab	Truxima	2017 (EMA); 2018 (US-FDA)	−Chronic GVHD therapy −Chronic GVHD prevention
	Rixathon	2017 (EMA)	
	Ritemvia	2017 (EMA)	
	Riximyo	2017 (EMA)	
	Blitzima	2017 (EMA)	
	Rituzena	2017 (EMA)	
Infliximab	Inflectra	2013 (EMA); 2016 (US-FDA)	−Acute GVHD therapy −Acute GVHD prevention
	Flixabi	2016 (EMA)	
	Remsima	2013 (EMA)	
	Renflexis	2017 (US-FDA)	
	Ixifi	2017 (US-FDA)	
	Zessly	2018 (EMA)	
Etanercept	Benepali	2016 (EMA)	−Acute GVHD therapy −Therapy for BOS and IPS.
	Erelzi	2016 (US-FDA); 2017 (EMA)	
Enoxaparin	Inhixa	2016 (EMA)	−DVT prophylaxis −DVT therapy
	Thorinane	2016 (EMA)	

EMA European Medicines Agency, *US-FDA* United States Food and Drug Administration, *GVHD* graft-versus-host-disease, *BOS* bronchiolitis obliterans syndrome, *IPS* idiopathic pulmonary syndrome, *DVT* deep venous thrombosis, *HCT* hematopoietic cell transplantation

[a]As of November 2018

[b]The only approved indication by both EMA and US-FDA for HCT

Below we discuss some of the possible uses of the approved biosimilars in the field of HCT (also presented in Table 2).

G-CSF analogs

There are many G-CSF analogs that include filgrastim, pegfilgrastim, and lenograstim. Filgrastim biosimilars were first approved in EU (2008) and the US (2015). Filgrastim is a human G-CSF with multiple indications. Our search strategy revealed that most articles in HCT discussed filgrastim biosimilars. Filgrastim is the only biosimilar with an approved HCT-related indication in both the EU and USA.

Three articles discussed other G-CSF analogs, including lenograstim and pegfilgrastim in addition to filgrastim [24–26]. Most HCT studies evaluated the role of filgrastim in autologous PBSC mobilization. Moreover, some studies evaluated its use in allo donors and in posttransplant neutrophil recovery. Most studies found no significant difference in the efficacy between the particular biosimilar and the original product. However, one study presented at ASBMT [27] reported the need for more doses of the biosimilar to achieve similar engraftment results with consequent longer period of neutropenia and increased antibiotic use. When cost analysis was included, costs reduction was reported with the biosimilars except in two studies in Japan and France [28, 29], the decrease in G-CSF costs were not reflected in reduced hospitalization costs. Two studies done in Mexico illustrated the similarity between filgrastim and its biosimilars. One study compared stem cell mobilization between ten patients receiving the biosimilar drug and nine patients receiving the originator product, the study found no significant difference between the two groups clinically on ten patients and found no significant difference [30]. While the other showed similar biochemical characteristics between the two products [31]. Another study from Jordan [32] presented in EBMT showed the similarity in efficacy between filgrastim and its biosimilar. Although small in sample size, more studies are needed from low-income countries, including the testing of locally produced biosimilars.

Rituximab

Rituximab is a monoclonal antibody against CD20, with multiple cancer-related indications [33]. The biosimilar rituximab has been approved in the EU in 2017, followed by the US in 2018. In 2010, it was listed as the second of the top 20 drugs contributing to outpatient expenditures in the US [8]. Because the pathogenesis of GVHD, highlights a role of B-cells, rituximab has been also studied for treatment of GVHD [34, 35] including steroid-refractory chronic GVHD [36]. Some data suggests possible efficacy using rituximab to decrease B-cell allogeneic immunity and as a steroid-sparing strategy in chronic GVHD [35, 37]. The recent approvals of rituximab biosimilars would allow conducting additional studies to investigate its safety and efficacy in HCT.

Anti-tumor-necrosis factor (TNF) drugs

TNF plays a role in the pathogenesis of GVHD and other inflammatory complications of HCT, including Bronchiolitis obliterans syndrome (BOS) [38]. The two biologics affecting TNF with approved biosimilars are infliximab and etanercept. As shown in Table 2, infliximab has six approved biosimilars in EU and USA, while etanercept has two approved biosimilars. Although several studies yielded negative results as treatment of GVHD, anti-TNF

drugs have shown some efficacy in pediatric patients [39–41]. Moreover, these drugs appeared beneficial in treating different pulmonary manifestations including BOS and IPS [42, 43]. Biosimilars of anti-TNF agents could potentially reduce costs substantially. For instance, etanercept is among five biologics with the highest total sales which being heavily used in rheumatological diseases [3, 8].

Challenges and opportunities

The economics of biosimilars in developing countries

Biosimilars are different from generic drugs. Biosimilars do not have the same chemical structure compared with their reference biological products, however, they have a similar structure with the same amino acid sequence [2, 21]. Thus, these structures will usually need more extensive comparability testing and clinical studies to confirm similar pharmacokinetics and efficacy, which means that the development of biosimilars will be substantially costlier than generic chemical drugs. The cost of developing and approving a biosimilar might reach $250 million (in USD) compared with 1–4 million for generic drugs, hence potentially limiting the impact of cost savings related to biosimilar availability [1, 5, 44]. Nonetheless, it is forecasted that biosimilars would still reduce the spending on biologics by around $54 billion USD (Range: $24–$150 billion), with a mean assumed decrease of 27% (Range: 9–51%) in the cost of biosimilars compared with the reference biological product [45].

Access to affordable health care is a challenge facing many economies. However, the challenge is greater in developing countries, hindering the access to basic health care and particularly to complex therapies such as, HCT and biologics [46]. Limited access to health care results from low income, high costs, political instability, lack of availability of general health care facilities, and specialized centers [46, 47]. Biosimilars have been shown to substantially decrease costs in developing countries. The introduction of rituximab biosimilar in India and Peru has led to 50% decrease in its costs [48]. By 2024, it is forecasted that the use of biosimilars for colony-stimulating factors and monoclonal antibody antineoplastics will result in 10% costs reduction [45]. A recent report by McKinsey & Company illustrates the projected biosimilars' annual market growth between 2018 and 2025 in emerging economies to be: 25–30% in Brazil, 15–20% in India, 10–15% in Mexico, Egypt, Vietnam, and Indonesia [49].

Table 3 Challenges facing introduction of biosimilars in developing world

Regulatory and legal challenges:
−Naming/defining biosimilars
−Defining guidelines for extrapolation and interchangeability
−Laboratory infrastructure to test biosimilar drugs
−Well-trained personnel
−Lack of funding
−Issues of intellectual property
Research and development challenges:
−Lack of infrastructure
−Difficulty in performing clinical studies, especially for complicated diseases, such as cancers
−Lack of funding
−Risks of decreased of efficacy and increased risks by extrapolating from developed countries published evidence
Educational barriers:
−Lack of knowledge about biosimilars: definition and possible uses
−Lack of confidence on guidelines for substitution, switching, and extrapolation
−Patient reluctance to receive biosimilars

Challenges facing biosimilars use in low- and lower-middle income countries

Compared with US-FDA and EMA, not all regulatory bodies in countries with restricted resources have developed and published guidelines regarding the approval of biosimilars. The EU pioneered the use of biosimilars, approving the first in 2006 [1]. In 2010, the Biologics Price Competition and Innovation Act under the Affordable Care Act paved the pathway for biosimilars approval in the US [1]. However, challenges to broader use of biologics and biosimilars (Table 3) include the complicated regulatory process, the need of educational initiatives and developing research infrastructure.

Regulatory and legal challenges

Cost and access to safe and effective drugs is essential to a successful health care strategy [50, 51]. Thus, the role of regulatory bodies is key to ensure and govern the access to quality medications. Regulatory bodies in developing countries may need added funding to support research and laboratory infrastructure and to retain well-trained personnel. In their article, Pezzola and Sweet [51], outlined a model to judge the quality of regulatory bodies in developing countries. They considered three domains; regulatory infrastructure, public quality control, and private market monitoring; and illustrated the global variation in those three domains. Many of developing countries' regulatory bodies adopt international standards and/or regional reference standards, rather than developing their own [50].

Table 4 Definition and regulatory information about biosimilar of different countries

Country	Defining biosimilarity	Reference drug conditions	Extrapolation of indications and interchangeability
United States [53]	"The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."	**"Reference product"** must be licensed by the US-FDA	**Extrapolation:** possible in context of "totality of evidence". MOA, PK, biodistribution, immunogenicity, and toxicity should be addressed. Sponsors are recommended to clinically study a condition that would detect any significant clinical difference. **Interchangeability:** Specific guidelines governing issues of Interchangeability are being developed
European Union [54]	A biosimilar medicine ("biosimilar") is a medicine highly similar to another biological medicine already marketed in the EU the so-called "reference medicine." Four features of biosimilars: (1) highly similar to the reference medicine, (2) no clinically meaningful differences compared with the reference medicine, (3) variability of biosimilar kept within strict limits, and (4) same strict standards of quality, safety, and efficacy	**"Reference medicine"** must be approved in the EU	**Extrapolation:** Possible after meeting the following criteria: (a) relevant study population (able to detect clinical difference). (b) Same mechanism of action mediated by same receptor. (c) Justified immunogenicity data (no automatic extrapolation). (d) Safety studies in one therapeutic indications. (e) Data across different clinical settings. **Interchangeability:** no recommendation on interchangeability is provided. Decisions on interchangeability are made on a national level
Brazil [55, 56]	"It is a biological product that was registered through compatibility exercises in terms of quality, efficacy, and safety."	**"Reference drug"** must be approved in Brazil or in countries with similar regulations	**Extrapolation:** permitted if there is a similarity in mechanism of action and the involved receptor of the different indications. **Interchangeability:** not addressed
Jordan [57]	"A biological medicinal product that is similar to the reference product in terms of quality, safety, and efficacy through the comparability studies, having the same active substance, dosage form, concentration, and route of administration of the reference product."	**"Reference product"** must be approved or registered in Jordan or in the reference countries in the EU based on full dossier	**Extrapolation:** not addressed. **Interchangeability:** biosimilars cannot be automatically substituted. Decisions to use should be made by a qualified health Professional
Egypt [58]	"Copy of a reference biological product having the same active substance, dosage form, concentration, and route of administration of a reference biological product and has proven through a comparability program that its quality, safety, and efficacy is highly similar to a reference product when prescribed in a claimed indication."	**"Reference biological Product"** should be licensed in Egypt or in a reference country (and widely marketed) for 2 years in a reference country based on full dossier	**Extrapolation:** Possible after meeting the following: (a) The study is made on a population that provide sensitivity to detect clinical difference. (b) Same MOA including receptor of action. (c) Immunogenicity and safety studies on the population that carries the highest risk of adverse effects. (d) Noninferiority design of efficacy studies. **Interchangeability**: not addressed
Saudi Arabia [59]	"New biological medicinal product claimed to be similar (Biosimilar products) in terms of quality, safety, and efficacy to a reference medicinal product (RMP), which has been granted a marketing authorization on the basis of a complete dossier."	**"Reference medicinal Product (RMP)"** must be registered at Saudi FDA or other stringent regulatory authority or to be innovator product	**Extrapolation:** not addressed. **Interchangeability**: not addressed
India [55, 60]	A similar drug in quality, efficacy, and safety to the reference biological product based on a comparability exercise	**"Reference biological Product"** should be licensed in India and innovator. If not licensed in India, then a 4 years license after approval from a country with a regulatory framework is needed	**Extrapolation:** possible after meeting the following: (a) the study is made on a population that provide sensitivity to detect clinical difference. (b) Same MOA including receptor of action. (c) Immunogenicity and safety studies on the population that carries the highest risk of adverse effects. (d) Noninferiority design of efficacy studies. **Interchangeability**: not addressed
Japan [61]	Biosimilars are biotechnology-applied pharmaceuticals that are developed by different manufacturers as biotechnology-applied pharmaceuticals which possess equivalent quality, safety, and efficacy with already approved as new biotechnology-applied pharmaceuticals in Japan	"**Reference preceding product**" must be approved by the Japan-PMDA	**Extrapolation:** the goal of the equivalence/ homogeneity assessment for biosimilars is to show high similarity in quality characteristics with preceding biopharmaceuticals, and in case of any differences in quality characteristics, it is required to show that the difference does not have adverse effects on the safety and efficacy of the final product. **Interchangeability**: no information provided

EU European Union, *US-FDA* United States Food and Drug Administration, *MOA* mechanism of action, *PK* pharmacokinetics, *PMDA* Pharmaceuticals and Medical Devices Agency

Some developing countries and emerging economies have published guidelines for biosimilars, for instance, final guidelines were published in Saudi Arabia (2010), Brazil (2010), Mexico (2012), India (2012), and Iran (2014). Moreover, drafted versions of guidelines were published in countries such as South Africa (2010), Venezuela (2012), Egypt (2012), and Jordan (2014) [52]. India has approved biosimilars of rituximab, filgrastim, pegfilgrastim, trastuzumab, and epoetin alfa [6]. Most of these guidelines are relatively recent and were published in the past 2 years. Table 4 illustrates the different aspects of biosimilars guidelines in the US and EMA, in comparison to those in Jordan, Egypt, Saudi Arabia, Brazil, and India [53–61]. It is noteworthy that the legal aspects of biosimilars is still to be developed even in high-income countries such as Saudi Arabia. There is a need for developing guidelines and protocols of approving biosimilars, including the need of bioequivalence studies and guidelines on switching between biosimilars, generic, and original medications in countries such as Saudi Arabia and Iran [62, 63].

Approving biosimilars is usually based on less extensive clinical studies that might involve some but not all

indications, thus raising concerns about extrapolation to existing indications for the reference product. Extrapolation allows the use of biosimilars in indications other than the one studied in clinical trials, which needs broad review of totality of evidence and its limitations [64]. Another important issue is interchangeability with the original biologic, which provides physicians or pharmacists the needed confidence to prescribe the biosimilar instead of the originating biologic without compromising efficacy and/or safety [64]. These should be defined and supported by a well-developed postmarketing surveillance system for the newly approved biosimilars.

Research and development infrastructure

Further research and development infrastructure is needed to develop biologics/biosimilars and support their safe testing and approval. Pharmacogenomics identifies the effect of our genetic make-up on response to drugs; and different populations/races may have distinct responses due to such inherent genetic variations [65, 66]. Optimally, well-performed trials in low- and lower-middle income countries would be able to confirm safety and clinical efficacy of drugs, including biologics/biosimilars. However, it will require time, infrastructure, expertise, and costs. Extrapolating data from countries of diverse ethnic groups might be safe, in addition to creating a postmarketing surveillance system for the newly approved biosimilars.

Research into these topics may be constrained by lack of qualified personnel, insufficient cultural awareness, as well as limited funding [67]. All these factors beg exercising caution when evaluating biologics and novel biosimilars in low and low-middle income countries. Thus, regional collaboration, through regional organizations can help to ensure the safety and efficacy of new agents and encourage regional or population-specific postmarketing analysis.

Educational barriers

Introducing biosimilars to markets is not an easy task. This is particularly true for complex diseases such as cancer, as patients may be unwilling to switch to biosimilars. This might introduce difficulties to perform clinical trials to determine the efficacy and safety of these new drugs. In a study involving more than one country, Jacobs et al. [68] reported low awareness among patients, with a relatively higher awareness in patients who are involved in advocacy groups.

Moreover, physicians and pharmacists might not feel comfortable prescribing biosimilars. A survey-based study involving physicians and other medical practitioners, showed the lack of knowledge about biosimilars and a low enthusiasm for prescribing them without additional information and education [8]. Low level of confidence for prescribing biosimilars was also reported among pharmacists [69]. In a more recent study involving over 1000 physicians from different specialties, Cohen et al. [70] showed the need to provide physicians with evidence-based informational materials pertaining to biosimilars. The study identified five areas that need further development including basics issues such as definitions to more sophisticated concepts such as interchangeability. Moreover, hematologists and oncologists had the greatest number of incorrect answers regarding biologics used in their field, indicating a gap in knowledge not only for biosimilars but also for biologics in general. Following the approval of multiple oncology-related biosimilar in the US, a recent study showed that the understanding of biosimilars is low [71]. The educational needs of low and low-middle income countries is yet to be studied, in one study involving multiple Middle Eastern and North African countries, around 65% of physicians (60% are from Lebanon) had knowledge about biosimilars, however, around 40% prescribe it [72].

These studies illustrate the urging need for educating and increasing awareness of biosimilars to patients, physicians, pharmacists, and the medical community at large. This places the bulk of responsibility on governments, regulatory bodies, and local societies to develop educational modalities and methods such as pamphlets, reports, conferences' lectures, and more importantly investing in social media platforms to provide physicians with up-to-date and evidence-based material. Having a focus on biosimilars within various professional HCT societies/organizations, including the ASTCT, EBMT, and other organizations in the low-income countries, will be important in educating medical practitioners.

Conclusions and future directions

Biosimilars hold a potential to lower costs for oncology and hematology related care, including HCT. Low- and lower-middle income countries, strategies to increase availability and use biosimilars would likely expand health care access. There is an ongoing dynamic approval of more biosimilars. This article is certainly not inclusive of all approved biosimilars, however, it highlights the different challenges and the opportunities offered by them. The regulatory, research, and educational barriers to wider use require health care practitioners and medical societies to:

- Define guidelines to help physicians and other health care practitioners understand the process of biosimilar approvals including definitions and education about the clinically significant topics of extrapolation and interchangeability. Systematic assessment of the impact of

biosimilars on costs and outcome should be performed periodically.
- Support local and regional research involving biologics to minimize risks associated with extrapolating data from other populations and collaboration to support multi-institutional studies, registries, and postmarketing surveillance systems.
- Promote education to increase awareness for patients and health care practitioners using social media, conferences, websites, and advocacy groups.
- Recognize changes in available biosimilars needing ongoing review of guidelines and existing clinical data.
- Understand the need of a holistic approach to cost-reduction in the field of HCT. Biosimilars is one of the potential strategies; however other strategies, including other commonly used drugs, such as antimicrobials (e.g. antifungals and antivirals), is also equally important.

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Compliance with ethical standards

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