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LEADING ARTICLE

Are Biosimilars the Future of Oncology and Haematology?

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Abstract
Biological drugs are vital but often high-cost components of cancer treatment. Several biosimilar versions of these drugs have been approved in Europe and/or the USA, with many more in development. However, there is some disconnect between the biosimilars that are approved for use and those accessible in clinical practice, with availability impacted by factors including patent litigation and complex healthcare insurance policies, particularly in the USA. Provided the barriers to widespread uptake can be overcome, biosimilars offer potential benefits including cost savings and improved patient access versus the reference product (RP). This article provides an up-to-date and focused perspective on the development and use of biosimilars in the haemato-oncology setting. European and US regulatory pathways governing biosimilar licensing demand that there are no clinically meaningful differences between a biosimilar and its RP. Pathways are rigorously enforced and involve comprehensive non-clinical evaluations and clinical trials in selected indications to establish the equivalence or non-inferiority of efficacy, and the comparability of safety, of the biosimilar versus its RP. 'Indication extrapolation' is only permitted if scientifically justifiable considering mechanism(s) of action, pharmacokinetics, immunogenicity and safety in relevant patient populations. Switching treatment from RP to biosimilar is supported by most available data, predominantly from indications other than cancer, and post-marketing pharmacovigilance programmes are warranted. Notably, the potential benefits of biosimilar cancer treatment may extend beyond direct cost savings: for example, the availability of biosimilars of common regimen components may help incentivise the evaluation and/or clinical use of new treatment approaches and novel drugs.

1 Introduction

Biological drugs are a cornerstone of treatment for advanced solid tumours and haematological malignancies. However, due to their structural complexity and production in living systems under strictly controlled conditions, biologicals are expensive to develop and manufacture. Consequently, treatment costs are usually high. For example, recently reported official list prices for rituximab reference product (RP) ranged from €410.76 in Belgium to €899.00 in Austria (2 × 100 mg) [1], while recent trastuzumab RP list prices ranged from €464.00 to €850.00 (150 mg) across 28 European countries [2]. Patent expiration for various cancer-targeting biologicals has enabled development of biosimilars: biological medicines that are highly similar to RPs that have gained regulatory approval [3, 4]. Since biosimilars are subject to abbreviated approval pathways versus RPs, the lower development costs are usually reflected in a discounted price once marketed. For example, in the British National Formulary, two rituximab biosimilars are priced at £314.33 each versus £349.25 for rituximab RP (100 mg/10 mL vial for infusion), while four trastuzumab biosimilars are priced at £366.66 each versus £407.40 for trastuzumab RP (150 mg powder for infusion) [5, 6], both representing a 10% discount. Estimates suggest that biosimilars will reduce direct spending on biologicals in the USA by US$24–150 billion between 2017 and 2026 [7], although the underlying assumption of constant RP pricing could be challenged by RP price increases prior to biosimilar launch [8] or price competition reducing RP costs [9].

In Europe and elsewhere, relatively structurally simple first-generation biosimilars have been prescribed to cancer patients for over a decade, often to prevent or counteract the side effects of chemotherapy [10]. For example, filgrastim-sndz (Zarxio; Sandoz, Princeton, NJ, USA) and filgrastim-aafi (Nivestym; Hospira, Inc., Lake Forest, IL, USA) are biosimilars of granulocyte colony-stimulating factor (G-CSF), commonly used to prevent or treat neutropenia following

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Key Points

With the first biosimilar licensed in Europe in 2006 and in the USA in 2015, biosimilars offer the opportunity to reduce the often high costs of biological therapy across many conditions.

Biosimilars of certain cancer-targeting biological drugs are now approved in the USA, Europe, and elsewhere, requiring proof that there are no clinically meaningful differences between biosimilar and reference product in comprehensive non-clinical evaluations and clinical trials.

Obstacles to biosimilar uptake, particularly in the USA, are threatening cost savings, despite their potential benefits being far-reaching: adoption of biosimilars of agents commonly used as the backbone of therapy into clinical practice and clinical trial treatment protocols could provide both direct savings and facilitate the use and/or evaluation of new treatment approaches and novel drugs.

chemotherapy, or in stem cell transplantation [11]. The introduction of such biosimilars has significantly impacted costs and access. By 2016, the average price per treatment-day of G-CSF therapy had decreased by 27% across the European Economic Area (EEA) compared with the year before biosimilar entry, and the overall cost of G-CSF therapy decreased by 8% and 62% (UK and Romania, respectively) [9]. Across Europe, the speed of biosimilar filgrastim uptake was linked to the nature of the market (hospital-based vs retail), and the extent influenced by local and regional policies within countries [12]. Patient access to G-CSFs also increased: compared with the year prior to biosimilar market entry, the volume of G-CSF therapy increased by 58% across EEA countries by 2016 [9]. A recent budget impact cost model predicted potential 5-year cost savings of US$256 million in the USA due to the availability of biosimilar G-CSFs [13], while another study simulating likely clinical scenarios in the USA estimated that US$5.6–8.5 million could be saved per 20,000 cancer patients receiving a course of biosimilar rather than reference filgrastim, enabling budget-neutral expanded access to filgrastim treatment or immunotherapies [14]. While a somatropin biosimilar (Omnitrope; Sandoz, Kundl, Austria) was the first biosimilar licensed by the European Medicines Agency (EMA) in 2006 [15], filgrastim-sndz was the first biosimilar approved by the US Food and Drug Administration (FDA) in March 2015 [16]. Biosimilar epoetins have been licensed in Europe since 2007, resulting in overall reductions in epoetin treatment cost [17, 18], while the first biosimilar epoetin was licensed by the FDA in 2018 [19].

Compared with first-generation biosimilars, the more complex structures and mechanisms of action (MoAs) of second-generation biosimilars permit use as cancer treatments rather than purely supportive care agents [10]. A biosimilar of the CD20-targeted monoclonal antibody rituximab (CT-P10, rituximab-abbs, Truxima; Celltrion, Incheon, Republic of Korea) was the first biosimilar cancer treatment approved by the EMA, in February 2017. Several other cancer-targeting biosimilars have been approved in Europe and the USA subsequently (Table 1), with further approvals expected over the coming years. Rituximab and trastuzumab biosimilars have gained regulatory approval for cancer indications in Japan [20, 21] and South Korea [22]; bevacizumab, rituximab, and trastuzumab biosimilars are licensed in Canada [23–27].

Biosimilars are set to become integral to cancer therapy. In this article, we discuss current and future issues related to biosimilar use in oncology and haematology, addressing key considerations important for physicians and other stakeholders in cancer care. We examine the evidence regarding biosimilar effectiveness in cancer treatment, including in extrapolated indications, and the appropriateness of switching from RP to biosimilar. We also consider the potential benefits of biosimilars in terms of cost savings and beyond, and highlight challenges to biosimilar uptake that restrict such benefits. We begin with a brief overview of the biosimilar development and regulatory approval processes, crucial to understanding these topics.

2 Development and Approval of Biosimilars

Although biosimilars are structurally highly similar to their RP, they cannot be identical due to natural variations in biologically produced macromolecules and possible differences in production processes between manufacturers [10, 28, 29]. Crucially, however, any slight differences between biosimilar and RP must only occur in clinically inactive components. Thus, the FDA defines a biosimilar as a "*biological product that is highly similar to and has no clinically meaningful differences [in terms of safety, purity, and potency (safety and effectiveness)] from an existing FDA-approved reference product*" [30]. The FDA further states that "*slight differences (i.e. acceptable within-product variations) are expected during the manufacturing process for biological products, regardless of whether the product is a biosimilar or a reference product*".

Biosimilars are subject to abbreviated approval pathways, like small molecule generic medicines [30, 31], aiming to reduce the time and costs required to provide additional treatment options for patients. However, the approach to

Table 1 Biosimilars currently approved by the FDA or the EMA for the treatment of solid tumours or haematological malignancies (as of September 4, 2019)

Reference product	Biosimilar (other names)	Manufacturer/company name	Approving agency	Marketed in Europe	Marketed in USA	Indications[a]	References
Bevacizumab	ABP 215 (bevacizumab-awwb; Mvasi)	Amgen/Allergan	FDA/EMA	No (patent protection expires 2022)	No (ongoing patent litigation with Genentech; court date June 2020)	*FDA*: Metastatic CRC Unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC Progressive glioblastoma Metastatic RCC Persistent, recurrent or metastatic cervical cancer *EMA*: Metastatic carcinoma of the colon or rectum Metastatic breast cancer Unresectable advanced, metastatic or recurrent non-squamous NSCLC Advanced and/or metastatic RCC Advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, including platinum-sensitive or platinum-resistant disease Persistent, recurrent or metastatic carcinoma of the cervix	[77, 92–95]
Trastuzumab	ABP 980 (Kanjinti)	Amgen/Allergan	EMA	Yes (launched in 2018)	N/A	Early or metastatic HER2-positive breast cancer Metastatic HER2-positive gastric cancer	[96, 97]
	CT-P6 (trastuzumab-pkrb; Herzuma)	Celltrion	FDA/EMA	Yes (launched May 2018)	No (expected launch 2020)	*FDA*: HER2-overexpressing breast cancer *EMA*: Early or metastatic HER2-positive breast cancer Metastatic HER2-positive gastric cancer	[99–101]
	MYL–1401O (trastuzumab-dkst; Ogivri)	Biocon/Mylan	FDA/EMA		No (launch delayed per licensing agreement between Mylan and Roche; expected launch 2019–2020)	*FDA*: HER2-overexpressing breast cancer HER2-overexpressing, metastatic gastric or gastroesophageal junction adenocarcinoma *EMA*: Early or metastatic HER2-positive breast cancer Metastatic HER2-positive gastric cancer	[102–104]
	PF-05280014 (Trazimera)	Pfizer	FDA/EMA	Yes (launched in Spain, April 2019)	No (settlement reached with Genentech; expected launch unknown)	*FDA*: HER2-overexpressing breast cancer HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma *EMA*: Early or metastatic HER2-positive breast cancer Metastatic HER2-positive gastric cancer	[105–108]
	SB3 (trastuzumab-dttb; Ontruzant)	Samsung Bioepis	FDA/EMA	Yes (launched March 2018 by MSD)	No (ongoing patent litigation with Genentech)	*FDA*: HER2-overexpressing breast cancer HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma *EMA*: Early or metastatic HER2-positive breast cancer Metastatic HER2-positive gastric cancer	[77, 109–111]

Table 1 (continued)

Reference product	Biosimilar (other names)	Manufacturer/company name	Approving agency	Marketed in Europe	Marketed in USA	Indications[a]	References
Rituximab	CT-P10 (rituximab-abbs; Truxima; Blitzima; Ritemvia)	Celltrion	FDA/EMA	Yes (launched in February 2017)	No (settlement reached with Roche; expected launch 2019)	*FDA*: NHL *EMA*: NHL CLL[b] Rheumatoid arthritis[b,c] GPA and MPA	[77, 112–117]
	GP2013 (Rixathon; Riximyo)	Sandoz	EMA	Yes (launched in June 2017)	N/A	NHL CLL[d] Rheumatoid arthritis GPA and MPA	[118–120]

CLL chronic lymphocytic leukaemia, *CRC* colorectal cancer, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *GPA* granulomatosis with polyangiitis, *HER2* human epidermal growth factor receptor 2, *MPA* microscopic polyangiitis, *MSD* Merck Sharp & Dohme, *N/A* not applicable, *NHL* non-Hodgkin's lymphoma, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma

[a]Please see cited product labels for full details of all indications

[b]Not Ritemvia

[c]Not Blitzima

[d]Not Riximyo

demonstrating biosimilarity is more complex than that warranted for demonstrating bioequivalence of a generic drug [30]. The FDA and EMA both advocate a stepwise approach to proving biosimilarity between a biosimilar candidate and its RP to enable regulatory or marketing authorisation approval, respectively [3, 4]. This involves the performance of analytical, non-clinical, and clinical studies, all directly comparing the biosimilar candidate and RP, using the same dosing protocol. Comparability in analytical and preclinical studies forms the foundation of biosimilarity for both the FDA and EMA, and pharmacokinetic evaluation in clinical studies is essential. However, other aspects of their approval pathways differ (Fig. 1). Analytical studies often require the greatest time and effort as they must be both comprehensive *and* highly sensitive to detect any differences between a biosimilar candidate and its RP in drug structure (post-translation modifications including glycosylation), biological activity (in vitro functions relevant to MoA, including target-receptor binding), or other product properties (protein concentration, host cell-related impurities) [32]. Subsequent non-clinical in vivo studies may evaluate pharmacokinetics, pharmacodynamics, toxicity, and/or immunogenicity [3, 4], although this is an area where FDA and EMA perspectives diverge (Fig. 1) [33].

Clinical trials are usually performed to prove that both the pharmacokinetics (more specifically, the bioavailability) and efficacy of the biosimilar candidate and RP are statistically equivalent (or non-inferior), and that no differences in pharmacodynamics, safety, or immunogenicity are apparent (Fig. 1). The FDA requires at least one clinical study comparing the immunogenicity of the biosimilar candidate and RP, recommending head-to-head comparison (which is required by the EMA) [4, 34]. Clinical experience with the RP should inform study design [4, 34], considering the nature and incidence of immune responses, including clinical relevance and severity of consequences [4]. Equivalence rather than non-inferiority trial designs are typically warranted to ensure that a biosimilar candidate possesses no clinically relevant increase in efficacy versus the RP. However, non-inferiority designs are acceptable in certain circumstances [4, 35]. Equivalence/non-inferiority margins must be protocol-specified, calculated based on clinically acceptable differences and considering variation observed in RP superiority trials [36, 37]. For both trial designs, statistical significance is typically assessed using confidence intervals (two-sided for equivalence and one-sided for non-inferiority trials) [36, 37]. Per the FDA, sample sizes must be adequate to allow detection of clinically meaningful differences between the biosimilar candidate and RP, and relevant safety signals [4]. Recruited study populations must have adequate sensitivity to identify any pharmacokinetic, pharmacodynamic, immunogenicity, or clinically meaningful differences between the biosimilar candidate and the RP,

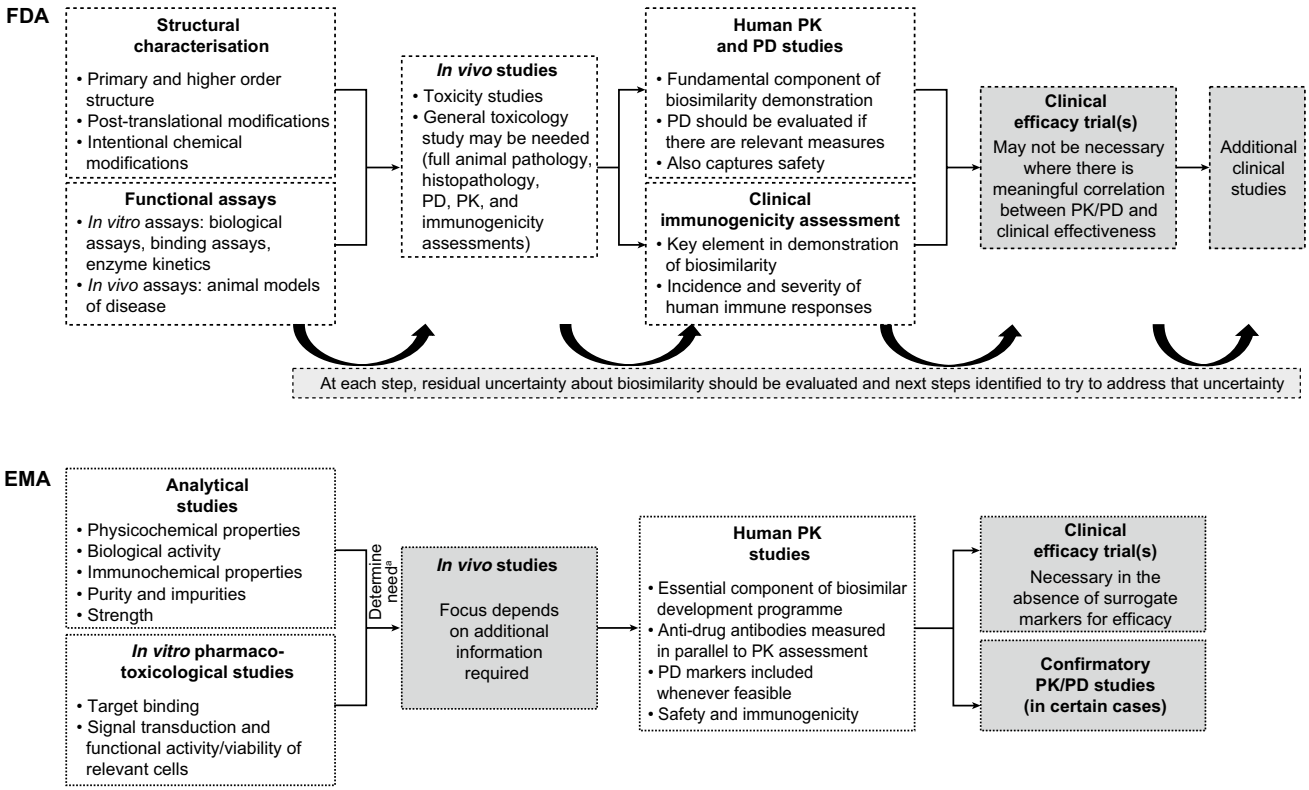

Fig. 1 Studies performed during development of a biosimilar as recommended by the EMA and FDA. The aim of a biosimilar development programme is to prove that there are no clinically meaningful differences between the biosimilar and its reference product. This is achieved via stepwise comparison of the two products in analytical, non-clinical, and clinical studies [4, 35, 91]. Grey boxes denote studies that may not be required. [a]The need for animal studies should be evaluated based on both the presence of, or quantitative differences in, potentially relevant quality attributes that were not detected in the reference product, and also relevant differences in formulation. *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *PD* pharmacodynamics, *PK* pharmacokinetics

and are often aligned with pivotal RP trials [4, 35]. Regulatory approval of a biosimilar candidate is granted only if the 'totality of evidence' from analytical, non-clinical, and clinical studies shows that there are no clinically meaningful differences from the RP.

Extrapolation, which permits licensing of a biosimilar in additional indications held by its RP without the need for further clinical trials, must also be considered. Extrapolation is only permitted if scientifically justifiable and supported by the totality of evidence: due consideration must be given and sufficient evidence provided regarding the RP MoA in each indication and the comparability of biosimilar and RP in relevant in vitro functional tests [4, 10, 38].

3 Are Biosimilars an Effective Option for Treatment with Curative Intent in Cancer?

The emergence of second-generation biosimilars means that biosimilars can be used to treat cancer patients with therapeutic, and indeed curative, intent, alongside the role of first-generation biosimilars in supportive care. Currently, five biosimilar cancer treatments have been approved by the FDA and eight by the EMA (Table 1)—all biosimilars of monoclonal antibody RPs (bevacizumab, rituximab, and trastuzumab).

As previously discussed, efficacy equivalence/non-inferiority is established in trials following demonstration of pharmacokinetic equivalence/non-inferiority. The efficacy objectives of a biosimilar trial differ from those of registrational trials for new drugs (which independently establish drug efficacy in a particular indication) [39]. Since objectives differ, trial designs differ. Endpoints traditionally used to confirm efficacy in cancer indications—such as progression-free survival, disease-free survival, and overall survival—are generally not necessary for detecting potential differences between a biosimilar candidate and its RP. These endpoints are indirectly influenced by patient-related factors including tumour burden, performance status, previous therapy, and subsequent treatment [38]. Instead, surrogate outcomes such as objective response rate (ORR) are considered sufficient as primary endpoints of biosimilar trials [38, 39]. Data on

survival outcomes are usually also collected, not least as these are particularly meaningful for patients.

Table 2 summarises published, or otherwise publicly available, primary efficacy endpoint data for approved biosimilar cancer treatments. The efficacy equivalence of ABP 215 (Mvasi; Amgen, Thousand Oaks, CA, USA) to bevacizumab was proven in a clinical trial assessing ORR (primary endpoint) in 642 patients with non-small cell lung cancer [40, 41]. Efficacy equivalence of trastuzumab biosimilars to RPs was established in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer in studies evaluating pathological complete response (pCR) or ORR as the primary endpoint [42–47]. In haematological malignancies, efficacy equivalence of the rituximab biosimilars CT-P10 and GP2013 (Rixathon/Riximyo; Sandoz) was evaluated in patients with follicular lymphoma (FL) in clinical trials assessing ORR (primary efficacy endpoint) [48–50]. Per regulatory requirements, these trials found no notable differences in safety profiles between biosimilar and RP.

To date, biosimilars approved for cancer treatment are generally licensed for all indications held by their RP (Table 1), as indication extrapolation was considered appropriate in these cases. For example, CT-P10 was compared with rituximab in clinical trials in patients with FL and rheumatoid arthritis (RA) [49–52], establishing pharmacokinetic and efficacy equivalence/non-inferiority, and no notable differences in safety. Similarity was also shown in functional tests related to the MoAs via which rituximab is believed to promote lysis of CD20-positive B cells (apoptosis, complement- and antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis), leading the EMA to conclude that the biosimilar and RP "*will have highly similar therapeutic effects across all indications*" and permit extrapolation of approval to other cancer indications (chronic lymphocytic lymphoma and diffuse large B-cell lymphoma) and non-cancer indications (two types of vasculitis) [53].

4 Is it Feasible to Switch from a Reference Product to a Biosimilar?

Approved biosimilars can be used in patients previously treated with the RP, as well as those not previously treated [54], meaning that patients undergoing treatment with a RP may, usually for cost-related reasons, be switched to receive an approved biosimilar instead. This situation is more likely to arise during maintenance rather than induction treatment in the cancer setting. Currently, data regarding the efficacy and safety of switching to approved biosimilar cancer treatments from respective RPs are scarce, with most existing data from non-cancer indications (specifically in RA for the rituximab biosimilars CT-P10 and GP2013) [55]. In the trial of the trastuzumab biosimilar ABP 980 in patients with HER2-positive early breast cancer, 725 patients treated with the RP during neoadjuvant treatment were randomised (1:1) after surgery to continue RP or switch to ABP 980 for the 1-year adjuvant phase. No increases in the frequency or severity of adverse events, or the incidence of anti-drug antibodies, were observed in the switch group. The percentage of patients with disease progression, recurrence, or death was similar between groups (switch 2.9%; continued RP 5.3%) [42, 55]. In the ongoing trial comparing CT-P10 with rituximab in 258 patients with low-tumour-burden FL ([50]; Table 2), all patients on RP will be switched to CT-P10 after the sixth of 12 maintenance phase cycles; data from the full maintenance phase are not yet available.

Considerably more studies have evaluated switching of biosimilars in non-cancer indications. A recent systematic literature review evaluated data from 14,225 patients enrolled in 90 studies that investigated the effects of switching from RP to first-generation biosimilars (including some used in supportive cancer care) or second-generation biosimilars used for the treatment of immune-mediated inflammatory diseases [56]. No differences in efficacy or safety were reported after switching in the majority of studies, including a randomised controlled trial funded by the Norwegian government that randomised 482 patients, whose inflammatory disease was stable during infliximab treatment, to either continue infliximab or switch to biosimilar CT-P13 [57]. No clinically relevant differences in safety or immunogenicity profiles have been identified in switching studies comparing filgrastim biosimilars and RPs in healthy volunteers or breast cancer patients [56, 58, 59], or for epoetin biosimilars/RPs in healthy volunteers or patients with kidney conditions [56, 60, 61].

Overall, available data on switching suggest that as long as biosimilarity has been established via a rigorous pathway such as those enforced by the FDA and EMA, switching from the RP to an approved biosimilar should be an acceptable approach. Nevertheless, further data collection is strongly encouraged, especially for biosimilar cancer treatments. Current position statements from the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) call for the treating physician, in close collaboration with the patient, to have responsibility for the decision whether or not to switch treatment [62, 63]. In the USA, however, the relative influence of clinicians versus other stakeholders (e.g. hospital pharmacy and therapeutic committees) on such decisions may vary and, in some cases, is still to be determined. In practice, European countries encourage substitution of RPs with biosimilars for treatment-naïve patients, and switching is largely recommended if conducted under the supervision of a healthcare professional (HCP) [64]. This is borne out in the high market share of biosimilar infliximab in Norway and Denmark, following the recommendation to switch by regulatory agencies

Table 2 Efficacy equivalence or non-inferiority of currently approved biosimilar cancer treatments and their reference products

Reference product	Biosimilar (other names)	Trial phase; patient population (N^a)	Study treatment[b]	Primary efficacy endpoint(s)	Primary efficacy endpoint data (biosimilar vs reference product)	References
Bevacizumab	ABP 215 (bevacizumab-awwb; Mvasi)	III; Stage IV or recurrent metastatic non-squamous NSCLC ($N=642$)	ABP 215 or reference bevacizumab (Avastin) iv (15 mg/kg Q3W for 6 cycles) (plus first-line carboplatin/paclitaxel chemotherapy)	ORR[c] during the study (duration of active treatment ~19 weeks)	ORR: 39.0% ($n/N=128/328$) vs 41.7% ($n/N=131/314$) 90% CI of RR for ORR (RR 0.93; CI 0.80, 1.09) were within prespecified equivalence margin (0.67, 1.5)	[40, 41]
Trastuzumab	ABP 980 (Kanjinti)	III; HER2-positive invasive early breast cancer ($N=696$)	Neoadjuvant ABP 980 or reference trastuzumab (Herceptin) iv (8 mg/kg loading dose, then 6 mg/kg Q3W for 3 cycles) (plus paclitaxel), following 4 cycles of run-in anthracycline-based chemotherapy	pCR[d] at time of surgery (within 3–7 weeks of final neoadjuvant study drug dose) based on local laboratory review of tumour samples	pCR: 48.0% ($n/N=172/358$) vs 40.5% ($n/N=137/338$) 90% CI of risk difference between treatments for pCR (difference 7.3%; CI 1.2, 13.4) were not within prespecified equivalence margin (− 13, 13) (upper bound was outside) 90% CI of RR for pCR (RR 1.188; CI 1.033, 1.366) were not within prespecified equivalence margin (0.759, 1.318) (upper bound was outside) Note: sensitivity analyses of pCR based on central laboratory review of tumour samples were performed: 47.8% ($n/N=162/339$) vs 41.8% ($n/N=138/330$) achieved pCR; 90% CI of risk difference and RR (difference 5.8%; CI − 0.5, 12.0; RR 1.142; CI 0.993, 1.312) were within the predefined equivalence margins	[42]
	CT-P6 (trastuzumab-pkrb; Herzuma)	III; HER2-positive stage I–IIIa operable early breast cancer ($N=504$)	Neoadjuvant CT-P6 or reference trastuzumab (Herceptin) iv Q3W (8 mg/kg loading dose [cycle 1], then 6 mg/kg for 7 cycles) (plus docetaxel [cycles 1–4] and FEC [cycles 5–8])	pCR[d] at time of surgery (within 3–6 weeks of final neoadjuvant study drug dose)	pCR: 46.8% ($n/N=116/248$) vs 50.4% ($n/N=129/256$) 95% CI of treatment difference (difference − 0.04; CI − 0.12, 0.05) were within prespecified equivalence margin (− 0.15, 0.15) 95% CI of RR for pCR (RR 0.93; CI 0.78, 1.11) were within prespecified equivalence margin (0.74, 1.35)	[43]
	MYL-1401O (trastuzumab-dkst; Ogivri)	III; HER2-positive metastatic breast cancer ($N=458$)	MYL-14010 or reference trastuzumab (Herceptin) iv Q3W (8 mg/kg loading dose, then 6 mg/kg for ≥ 7 cycles) (plus docetaxel or paclitaxel)	ORR[c] at week 24	ORR: 69.6% ($n/N=160/230$) vs 64.0% ($n/N=146/228$) 90% CI of rate ratio for ORR (ratio 1.09; CI 0.974, 1.211) were within prespecified equivalence margin (0.81, 1.24) 95% CI of treatment difference for ORR (difference 5.53%; CI − 3.08, 14.04) were within prespecified equivalence margin (− 15, 15)	[44]
	PF-05280014 (Trazimera)	III; HER2-positive metastatic breast cancer ($N=707$)	PF-05280014 or reference trastuzumab (Herceptin) iv (4 mg/kg loading dose, then 2 mg/kg QW) for ≥ 33 weeks (plus paclitaxel)	ORR[c] by week 25 and confirmed by week 33	ORR: 62.5% ($n/N=220/352$) vs 66.5% ($n/N=236/355$) 95% CI of RR for ORR (RR 0.940; CI 0.842, 1.049) were within prespecified equivalence margin (0.80, 1.25)	[46, 47]

Table 2 (continued)

Reference product	Biosimilar (other names)	Trial phase; patient population (N^a)	Study treatment[b]	Primary efficacy endpoint(s)	Primary efficacy endpoint data (biosimilar vs reference product)	References
	SB3 (trastuzumab-dttb; Ontruzant)	III; HER2-positive stage II–III early breast cancer ($N=800$)	Neoadjuvant SB3 or reference trastuzumab (Herceptin) iv Q3W (8 mg/kg loading dose [cycle 1], then 6 mg/kg for 7 cycles) (plus docetaxel [cycles 1–4] and FEC [cycles 5–8])	bpCR[e] at time of surgery	bpCR: 51.7% ($n/N=208/402$) vs 42.0% ($n/N=167/398$) 95% CI of adjusted ratio for bpCR rates (ratio 1.259; CI 1.085, 1.460) were within prespecified equivalence margin (0.785, 1.546) 95% CI of adjusted difference for bpCR (difference 10.70%; CI 4.13, 17.26) were not within prespecified equivalence margin (− 13, 13) (upper bound outside) Note: authors stated that efficacy equivalence was demonstrated based on the ratio of bpCR rates	[45]
Rituximab	CT-P10 (rituximab-abbs; Truxima; Blitzima; Ritemvia)	III; advanced (Ann Arbor stage III–IV) follicular lymphoma ($N=134$)	CT-P10 or reference US-sourced rituximab (Rituxan) iv (375 mg/m^2 Q3W for 8 cycles plus CVP ["induction period"])	ORR[f] over 24 weeks (induction period)	ORR: 97.0% ($n/N=64/66$) vs 92.6% ($n/N=63/68$) One-sided 97.5% CI of the treatment difference for ORR (difference 4.3%; CI − 4.25) lay on positive side of predefined non-inferiority margin (− 7)	[49]
		III; low-tumour-burden (Ann Arbor stage II–IV) follicular lymphoma ($N=258$)	CT-P10 or reference US-sourced rituximab (Rituxan) iv (375 mg/m^2 QW for 4 cycles ["induction period"], then Q8W for 6 cycles ["maintenance period"])	ORR[f] by month 7 (before cycle 3 of maintenance period)	ORR: 83.1% ($n/N=108/130$) vs 81.3 ($n/N=104/128$) 90% CI of treatment difference for ORR (difference 1.8%; CI − 6.43, 10.20) were within prespecified equivalence margin (− 17, 17)	[50]
	GP2013 (Rixathon; Riximyo)	III; Ann Arbor stage III–IV advanced follicular lymphoma ($N=624$)	GP2013 or reference EU-licensed rituximab (MabThera) iv (375 mg/m^2 Q3W for 8 cycles plus CVP ["combination therapy phase"])	ORR[g] over 24 weeks (combination therapy phase)	ORR: 87.1% ($n/N=271/311$) vs 87.5% ($n/N=274/313$) 90% and 95% CI of treatment difference for ORR (difference − 0.4%; 90% CI − 5.10, 4.30; 95% CI − 5.94, 5.14) were within prespecified equivalence margin (− 12, 12)	[48]

bpCR breast pathological complete response, *CI* confidence interval, *CVP* cyclophosphamide, vincristine, and prednisone or prednisolone, *EU* European Union, *FEC* fluorouracil, epirubicin, and cyclophosphamide, *HER2* human epidermal growth factor receptor 2, *iv* intravenous, *NSCLC* non-small cell lung cancer, *ORR* objective response rate, *pCR* pathological complete response, *QW* every week, *Q3W* every 3 weeks, *Q8W* every 8 weeks, *RR* risk ratio

[a] N = total number of study patients in whom primary efficacy endpoint was assessed

[b] Study treatment related to primary efficacy endpoint (some patients in studies shown in the table could continue in the studies beyond the time of primary endpoint assessment, sometimes with different treatments offered beyond those shown in the table)

[c] Proportion of patients with complete response or partial response according to Response Evaluation Criteria in Solid Tumours v1.1 [121]

[d] Absence of invasive cancer in breast and axillary lymph nodes, regardless of ductal carcinoma *in situ*

[e] No histological evidence of residual invasive tumour cells in the breast

[f] Proportion of patients with complete response, unconfirmed response, or partial response according to 1999 International Working Group response criteria [122]

[g] Proportion of patients with complete response or partial response according to 2007 revised response criteria for malignant lymphoma [123]

and HCPs, while the opposition to switching by Sweden's drug authority has reduced biosimilar uptake [65].

When discussing switching from a RP to a biosimilar, it is important to consider the concept of 'interchangeability', although differences in terminology between the EMA and FDA have caused some confusion [64]. The EMA describes interchangeability as exchanging between a RP and a biosimilar (or vice versa) or two biosimilars, either by prescriber-led switching or auto-substitution at the pharmacy level [66]; whereas section 351(k) of the US Public Health Service Act (PHSA) states that an interchangeable product "*may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product*" [67]. Final FDA guidance on demonstrating interchangeability has recently been published [68], clarifying that biosimilars should meet the interchangeability standard under the PHSA. The FDA guidance also specifies that at least one switching study, involving at least two alternating exposures to the RP and proposed interchangeable biosimilar, would normally be required to demonstrate interchangeability [68]. Following FDA designation as interchangeable, US state laws will regulate the ability of pharmacists to substitute a biosimilar for the RP. Although the FDA has yet to make such a designation, the majority of US states have already passed relevant legislation [69]. The final FDA guidance could pave the way for approval of interchangeable products, although ASCO has raised concerns about the possibility of 'automatic' substitution without physician intervention [70]. The EMA, meanwhile, "*does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar*": this responsibility falls to EU Member States [66]. However, Member States are referred to the scientific evaluations performed by the EMA scientific committees to support such decision making [66]. In Canada, the authority to declare a biosimilar interchangeable with its RP rests with individual provinces and territories [71], while Japanese regulations do not address this issue [12].

5 Benefits of Biosimilars: Potential for Cost Reductions, Increased Patient Access, and Beyond

The availability of new biosimilars offers the potential for direct cost savings through lower list prices and/or stimulation of price reductions in the RP and any competitor biosimilars, potentially enabling increased patient access to biologicals. Simulations show that adopting biosimilar filgrastim or epoetin in supportive cancer care would enable a budget-neutral expansion of access to biological cancer therapies [14, 72], illustrating wider benefits of biosimilar uptake in the healthcare system. The ability to enter the market at a lower list price is undoubtedly a key driver of biosimilar development, although price discounting of biosimilars relative to RP, and the resulting impact on biosimilar uptake, varies between countries [12]. Anticipatory RP price increases prior to biosimilar launch may restrict overall cost savings [8], and competitive price reductions for the RP could limit return on investment for biosimilar developers. Indeed, revenue from the epoetin alfa RP remains high despite FDA/EMA approval of several biosimilars [73], and cost savings from biosimilar filgrastim have been lower than expected in the USA [74]. The paucity of biosimilar competitors in the USA, unlike in the EU, as well as dominant biological manufacturers developing biosimilars, reduces price competition [8, 75]. Additional challenges to biosimilar uptake also impact cost savings, considered in section 6.

However, benefits may extend beyond direct cost savings in this era of biosimilar cancer treatments. For example, combination biological therapy may see increased uptake, where appropriate, including combinations using the RP alongside an approved biosimilar. Innovation to optimise existing treatment strategies or to develop novel strategies involving currently available agents may be encouraged by the availability of biosimilars of drugs commonly used as the backbone of therapy (e.g. bevacizumab, rituximab). This may be particularly true for investigator-initiated studies, where the potential costs of study treatments may be prohibitive. Biosimilar availability also has the potential to reduce the costs associated with performing clinical trials of novel drugs, biological or otherwise.

6 Challenges for Biosimilar Uptake

While several biosimilars have been launched in Europe, to the best of our knowledge, none of the biosimilars licensed by the FDA for the treatment of solid tumours or haematological malignancies have been launched in the USA to date (Table 1). Patent protections and the 12-year market exclusivity period provided under the Biologics Price Competition and Innovation Act (BPCIA) are inhibiting biosimilar uptake in the USA [8, 76]. Following US launch in 2015, biosimilar filgrastim faced patent infringement proceedings and litigation under the BPCIA [12]. Ongoing patent litigation facing many licensed second-generation biosimilars, combined with 'pay for delay' patent settlements resulting in later biosimilar launch dates [77, 78], is hindering US biosimilar market entry (Table 1). Until quite recently, patent settlements have been undisclosed; however, the Patient Right to Know Drug Prices Act, introduced in 2018 [79], dictates that settlement agreements regarding the manufacture, marketing, or sale of biological and biosimilar products must now be disclosed to regulatory authorities [80].

There are further obstacles to biosimilar uptake post-launch. For inpatient or hospital pharmacy use, biosimilars must be added to the formulary, and for interchangeable products, auto-substitution will likely favour the product deemed most cost effective [81]. In the community, product selection is driven by patients' health plans [81], and the designation of biosimilars as non-preferred by many health plans will limit uptake [82]. Independent physician practices must balance purchase costs with reimbursement, which could lead to financial incentives for continued RP use if margins are greater, despite higher RP list prices [81]. Reimbursement for patients must also be appropriate. While this is the case for Medicaid, a coverage gap in Medicare means that the out-of-pocket costs of biosimilars will exceed those of the RP for some patients [83]. If not amended by legislation, Lyman et al argue that this issue may limit biosimilar use and negate any cost savings [83].

Physician and patient perceptions also impact biosimilar uptake globally, and ongoing HCP education and provision of patient information is warranted [62, 83, 84]. Indeed, a recent ESMO survey identified strong demand for educational activities regarding biosimilars among prescribing physicians [85]. ASCO has recently reaffirmed its commitment to ongoing biosimilar-related prescriber and patient education, noting that the treating physician is the best source of information for patients [62].

Safety concerns previously arising with biologicals in oncology and haematology may impact physician confidence in biosimilars. For example, formulation changes leading to increased immunogenicity in the epoetin RP Eprex® (Janssen-Cilag Limited, High Wycombe, UK) were associated with a spike in pure red cell aplasia (PRCA) cases in Europe in 1998–2004 [86]. Later PRCA reports with biosimilar epoetins were linked to increased immunogenicity due to manufacturing and storage issues [86, 87]. Thus, the safety and immunogenicity of all biologicals requires ongoing evaluation through post-marketing pharmacovigilance programmes. This is reflected in the EMA's requirement for biosimilar developers to describe the pharmacovigilance system and risk-management plan, specifically addressing immunogenicity, during the authorisation procedure. Both the EMA and FDA indicate that post-marketing safety monitoring should be tailored to reflect risks identified with the RP [4, 35]. Reassuringly, no differences have been identified in safety profiles of biosimilar and RP epoetins or filgrastims over the relatively long European post-marketing experience [86], and a recent analysis of adverse event reporting for Sandoz-manufactured biosimilars and biosimilars in Denmark found that current reporting practices are able to attribute events to a specific biologic or biosimilar in most cases [88].

7 Summary and Future Perspectives

Biological drugs are vital but often high-cost components of cancer treatment, with European list prices set at tens of thousands of Euros per treatment course [1]. The prices of new cancer drugs at launch have risen in recent years [89], alongside the introduction of high-cost therapies such as chimeric antigen receptor T-cell therapy [90]. The costs of well-established biologicals have also increased [89]. Thankfully, as patents for the first wave of biological cancer drugs have expired, biosimilars are emerging to augment the oncology therapeutic armamentarium. Such biosimilars have the potential to deliver significant cost savings, although variations in price discounting and challenges to biosimilar uptake, particularly in the USA, are limiting access to these treatments.

Regulatory approval of a biosimilar candidate is granted once analytical, non-clinical, and clinical studies have proven that there are no clinically meaningful differences versus the RP. Evidence collected during development must include proof of the statistical equivalence or non-inferiority of pharmacokinetics, and usually clinical efficacy. For biosimilar cancer treatments approved to date, evidence has been gathered in clinical trials performed in patients with breast cancer, non-small cell lung cancer, or FL. Although these trials have correctly adopted surrogate markers of efficacy such as pCR and ORR as their primary endpoints, physicians and patients will welcome publication of survival data from such trials. Publication of 'real-life' data on the efficacy and safety of biosimilar cancer treatments is also anticipated, especially in extrapolated indications, although extrapolation is only permitted when scientifically justified and supported by the totality of evidence collected during biosimilar development. Valuable real-world data will also be gathered via company pharmacovigilance plans implemented after biosimilar approval.

Data on first- and second-generation biosimilars that have been approved for some years support the conclusion that switching a patient whose disease is stable during treatment with a RP to a rigorously developed and approved biosimilar should not be associated with adverse clinical consequences. Nevertheless, each case should be considered on its own merit, with the treating physician leading the decision-making process. Notably, data regarding switching between different biosimilars of the same RP are currently very limited. As the number of approved biosimilars rises, however, such data will be required. Whether interchangeable versions of biological cancer drugs will be approved in the future remains to be determined, not least as the validity of 'multiple switching' is highly debated within oncology and haematology.

It is hoped that the availability of biosimilar cancer treatments will encourage further innovation and research around treatments for solid tumours and haematological malignancies. It will be especially interesting to note whether future clinical trials take advantage of available biosimilars, incorporating these into combination therapy regimens. Biosimilars of other drugs will become available in the future due to continued patent expiry and loss of exclusivity protection; for example, biosimilars of the epidermal growth factor receptor inhibitor, cetuximab, are already in development.

For the potential benefits of biosimilar cancer treatments to be fully realised, several measures will need to be taken to change stakeholder perceptions and encourage acceptance and uptake, including targeted education, collection of real-world efficacy and safety data, and pharmacoeconomic analyses. Inclusion of biosimilars in treatment guidelines will also influence physician acceptance. Of course, the perspectives and needs of patients should remain the primary concern. In this regard, education on the (lack of) differences between a biosimilar and its branded RP will be essential, as will clear signposting of the potential personal and societal benefits of biosimilars in terms of reduced costs and/or increased treatment access. Additional barriers to the marketing and uptake of biosimilars specific to the USA must also be addressed to attain the full benefits of biosimilars.

8 Conclusions

Biosimilars have arrived in the cancer therapeutic space. The impact of these agents on patient care will, we hope, be great. Marked reductions in the direct costs of treatment are possible if challenges to biosimilar uptake can be overcome, helping more patients receive optimal cancer care. Other benefits, such as incentivising the evaluation or use of new treatment approaches and novel drugs, are also keenly anticipated.

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