REVIEW

An Introduction to Biosimilars for the Treatment of Retinal Diseases: A Narrative Review

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ABSTRACT

Biological therapies have revolutionized the treatment of disease across a number of therapeutic areas including retinal diseases. However, on occasion, such treatments may be relatively more expensive compared to small molecule therapies. This can restrict patient access and treatment length leading to suboptimal clinical outcomes. Several biosimilar candidates of ranibizumab and aflibercept are currently in development and the first biosimilar of

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ranibizumab received EMA approval in August and FDA approval in September 2021. Biosimilars are biological medicines that are highly similar to an already-approved biological medicine (reference product). The physicochemical and clinical similarity of a biosimilar is determined by a rigorous analytical and clinical program, including extensive pharmacokinetic and pharmacodynamic analysis with phase III equivalence studies where appropriate. These phase III studies are carried out in a patient population that is representative of all of the potential approved therapeutic indications of the originator product and the most sensitive for detecting potential differences between the biosimilar and the reference product. Biosimilars have been used successfully across a wide range of therapeutic areas for the past 15 years where they have achieved substantial cost savings that can be reinvested into healthcare systems without affecting the quality of patient care. The current review provides an introduction to biosimilars with the aim of preparing retinal specialists for discussing these products with their patients.

Key Summary Points

Anti-VEGFs are highly effective within retinal diseases but cost can potentially limit the intensity or length of therapy and thereby provide suboptimal clinical outcomes.

Biosimilar candidates of ranibizumab and aflibercept are currently in development for the treatment of retinal diseases and some have received regulatory approval.

The physicochemical and clinical similarity of a biosimilar to its reference is determined by a rigorous analytical and clinical program including phase III equivalence studies where appropriate.

Biosimilars may optimize clinical outcomes while providing substantial cost savings that can be reinvested into healthcare systems.

The current review provides an introduction to biosimilars with the aim of preparing retinal specialists for discussing these products with their patients.

INTRODUCTION

The introduction of recombinant biological therapies has transformed treatment across a wide range of therapeutic areas including oncology, endocrinology, immune-mediated inflammatory disorders, kidney disease, and supportive care [1–6]. Biological therapies have also significantly improved outcomes in the treatment of neovascular retinal disorders [7], where recombinant proteins targeting vascular endothelial growth factors (VEGFs) are now considered first-line treatment options [8].

While undoubtedly effective, biologics are associated with high costs driven by the expense of their development [9, 10]. These high costs can lead to clinical unmet needs such as delayed treatment access or worsening disease activity in patients with rheumatoid arthritis (RA) [11, 12], restriction of treatment to those patients with RA who have severe disease [13, 14], and potentially premature cessation of therapy in patients with psoriasis or psoriatic arthritis [15].

Biosimilars are biological medicines that are highly similar to, and have no clinically meaningful differences from, an already-approved biological medicine (reference product) that may provide patient access at a reduced cost [16]. They have become established treatment options for diseases such as RA, psoriasis, cancer, and inflammatory bowel disease [17–19], and there are 82 biosimilars currently approved in the EU and 29 in the USA (Fig. 1; [20, 21]). Biosimilars have been shown to provide cost savings across therapeutic areas and at all levels of the healthcare system and such cost savings can be used to treat more patients and or invested in clinical services to improve patient care [22].

Biosimilars have recently entered the ophthalmology field for the treatment of neovascular retinal diseases and are expected to lead to reductions in expenditures on anti-VEGF treatments [23, 24]. While some retinal specialists may have gained experience in using biosimilars when treating non-infectious uveitis with biosimilar adalimumab, not all clinicians may be familiar with these products [25–28].

This review aims to provide an introduction to biosimilars for retinal specialists: how they are developed; their regulatory approval pathway; and how they can best be leveraged to optimize the management of neovascular retinal diseases in clinical practice. Experience from other therapeutic areas has shown that comprehensive, relatable, and timely education on biosimilars, in addition to clinical experience, is critical to their widespread and well-informed adoption [29]. The article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.
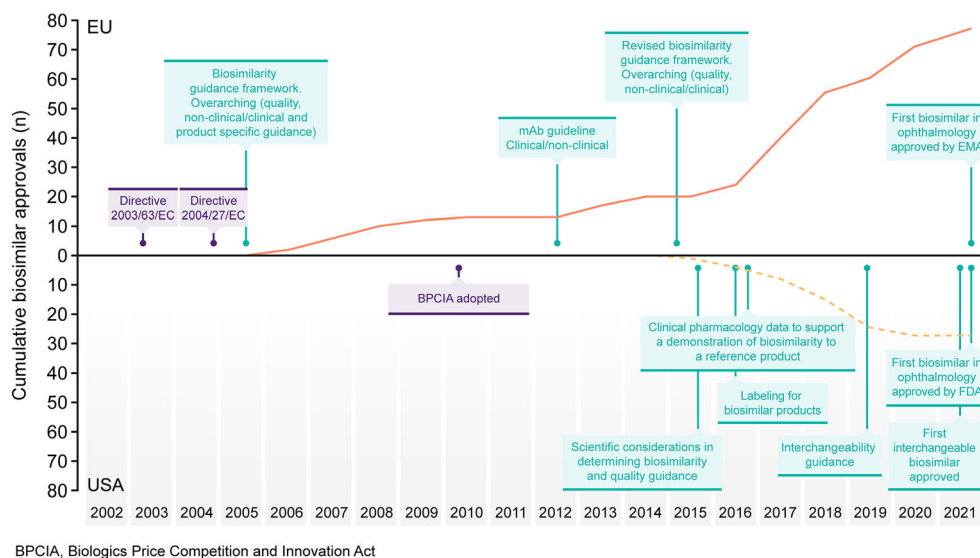
Fig. 1 Key biosimilar legislation and guidance development and biosimilar cumulative approvals in the EU and USA

WHAT ROLE MAY BIOSIMILARS PLAY IN THE OPHTHALMOLOGY SPACE?

Of an estimated global drug budget of US $1 trillion in 2018, innovative biologics accounted for 29% (US $296 billion [30]). In ophthalmology alone, the annual Medicare drug costs for ranibizumab averaged $1.3 billion between 2011 and 2015, and the costs of aflibercept averaged $1.4 billion between 2013 and 2015. Combined, ranibizumab and aflibercept accounted for 12% of the Medicare Part B budget annually [31]. In attempts to reduce the cost of, and increase access to, anti-VEGFs within neovascular retinal diseases, physicians have turned to using off-label bevacizumab (it is currently indicated for solid tumors only [32]). Bevacizumab appears generally non-inferior to ranibizumab and aflibercept in neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME), although a recent trial in retinal vein occlusion (RVO) could not conclude that bevacizumab was non-inferior to aflibercept [33–36]. Also, ziv-aflibercept, an anti-VEGF drug approved for treating colorectal cancer, has been investigated as a treatment for nAMD [37], despite the fact that in the EU intravitreal use of ziv-aflibercept is contraindicated because of its hyperosmotic properties [38]. In addition to their off-label-driven limitations, both products require additional compounding prior to use in retinal diseases, which may increase the risk of intraocular infections [39–42].

High acquisition costs and consequent access restriction can lead to potential vision complications or vision loss in vulnerable ophthalmology patient groups [43] and across all socioeconomic situations. In the LUMINOUS study, a global real-world study on treatment practices for ranibizumab in nAMD, 72.9% of patients received six or fewer injections in the first year and 35.5% of patients received three or fewer. The same study demonstrated that treatment outcomes correlated to the number of injections given, such that the greater the number of injections given, on average, the better the visual outcome [44]. The authors suggested that undertreatment may be linked to several factors including reimbursement of treatment, limited medical insurance coverage, and limited access to treatment and high treatment cost. In the USA the presence of a co-pay decreased the odds of patients with DME receiving anti-VEGF therapy (by 40%) and also decreased the odds of the patient following up (by 37%) [45]. In another study from Australia, lower out-of-pocket costs were associated with

higher adherence and compliance rates for anti-VEGF therapy in patients with AMD or DME [46]. Treatment costs may have an even greater impact in low- and middle-income countries. A single-center, retrospective review of 648 patients with retinal diseases from India showed that over half of patients were lost to follow-up. The most common reason given was unaffordability (41%) with the proportion of patients stating this increasing with the number of treatment injections given [47]. Undoubtedly, there is a need to provide more affordable and cost-effective anti-VEGF treatments for neovascular retinal diseases globally.

The introduction of biosimilars has been shown to reduce costs across a range of therapeutic areas. Table 1 provides an overview of some modelling and real-life studies showing the cost savings possible through the use of biosimilars within rheumatology, gastroenterology, dermatology, oncology, and supportive care. These savings increased when biosimilars were used for longer and over a larger number of patients. The majority of studies also calculated that these cost savings could result in tens of thousands of additional patients being treated with biologics, which could increase substantially should the benefits of biosimilars be available more widely. There is no reason to believe that biosimilars could not have a similar effect with ophthalmology.

REGULATION, DEVELOPMENT, AND APPROVAL OF BIOSIMILARS

The evolution of biosimilars within the EU began in 2004 when Directive 2004/27/EC provided legal basis for the definition of what biosimilars are, followed by the development of guidelines covering overarching principles, quality attributes, non-clinical/clinical requirements, and product-class specific items (Fig. 2). Biosimilars are different from generics in that generic versions of simple, chemically synthesized compounds are created by predictable chemical processes whereas biosimilars are manufactured using complex processes using living cell lines and require a comprehensive approval process [16]. For biosimilars,

the development time is significantly longer, the development costs are significantly higher, and the manufacturing process requires a higher level of expertise compared with that needed for generic compounds [48]. A typical small molecule generic drug will take 3–5 years to develop and costs $1–5 million, while a biosimilar may take around 8 years and costs $100–200 million to develop. In comparison, a novel originator biologic takes 12 years or more to develop with costs in excess of £1 billion [49, 50].

In order to gain regulatory approval, biosimilars are required to demonstrate a high degree of similarity to the originator molecule in terms of quality characteristics, biological activity, safety and efficacy, based on a comprehensive comparability exercise [51–54]. The foundation of the biosimilarity exercise is a thorough side-by-side analysis of the quality attributes of the biosimilar and its reference product [55]. The techniques used to analyze quality characteristics have improved continually over the past decade in terms of accuracy and sensitivity which allows biosimilar manufacturers detect and characterize differences between two products with high degrees of certainty [56, 57]. Several complementary methods are used to determine the quality "fingerprint" of a biosimilar with an emphasis of so-called critical product quality attributes (CQAs), which are the chemical, physical, biological, and microbiological characteristics that can be defined, measured, and continually monitored to ensure that the final product outputs remain within acceptable limits of quality (Fig. 2) [58, 59]. Minor structural differences between the biosimilar and the reference biologic may be present as long as these have no clinically relevant impact. Such differences occur commonly for originator biologics and are inherent to manufacturing in biological expression systems, and may also be affected by changes to their manufacturing process, such as cell line/cell culture media, or equipment changes [60]. Regulators have a great deal of experience in dealing with such manufacturing changes, which are considered acceptable as long as it can be supported that the changes do not impact the efficacy or safety of the product.

Table 1 Potential savings as a result of biosimilar introduction within the EU (adapted from Rezk and Pieper, 2020 under a Creative Commons Attribution-NonCommercial 4.0 International License: https://creativecommons.org/licenses/by-nc/4.0/)

| References	Country	Therapy area	Biosimilars	Model	Projected saving	Additional patients treated
Aladul et al. [128]	UK	Rheumatology/gastroenterology	Adalimumab, etanercept, infliximab	Budget impact model using retrospective market shares of biologics in rheumatology and gastroenterology	£44 million over next 3 years	
Jha et al. [129]	Belgium Germany Italy Netherlands UK	Rheumatology/gastroenterology/dermatology	Infliximab	Budget impact model with a 1-year time horizon	€25.79–77.37 million depending on country and price discount	1960–7561 across all five countries
Brodszky et al. [130]	Bulgaria Czech Republic Hungary Poland Romania Slovakia	Crohn's disease	Infliximab	3-year, prevalence-based budget impact analysis	Scenario 1: interchanging not allowed: €8 million Scenario 2: interchanging allowed in 80% patients: ~ €17 million	

Table 1 continued

References	Country	Therapy area	Biosimilars	Model	Projected saving	Additional patients treated
Lee et al. [131]	28 EU countries[a]	Breast cancer Gastric cancer	Trastuzumab	Budget impact model with time horizon of 1–5 years	€0.91–2.27 billion over 5 years depending on scenario. In the first year only budget savings ranged from €58 to €136 million	3503–7078
Gulacsi et al. [132]	28 EU countries[a]	Rheumatology and cancer	Rituximab	3-year base-case scenario	Base-case scenario (biosimilar uptake 30%, cost 70% of originator): €90 million. Second scenario (biosimilar uptake 50%): €150 million	Over 3 years projected budget savings were €570 million equating to 47,695 additional patients able to access rituximab
MacDonald et al. [133]	USA	Hematology	Pegfilgrastim	Budget impact model over 6 cycles	Converting 50% from reference pegfilgrastim to biosimilar would save $10.2 million per cycle and $60.9 million over 6 cycles	Over 6 cycles 2638–15,829 additional doses of pegfilgrastim biosimilar could be provided

Table 1 continued

References	Country	Therapy area	Biosimilars	Model	Projected saving	Additional patients treated
Yang et al. [134]	USA	Oncology	Bevacizumab	Budget impact model with time horizon of 1–5 years	Cumulative 5-year cost savings were $7,030,924 for a commercial payer and $4,059,257 for Medicare	Savings would allow 12 additional patients to have access to a 1-year treatment course of bevacizumab biosimilar
Yang et al. [135]	France	Oncology	Pegfilgrastim	Budget impact model with time horizon of 1–5 years	Total cumulative annual cost savings €3,518,669 over 5 years	N/A
Jang et al. [136]	France Germany Italy Spain UK	Oncology	Rituximab Trastuzumab	Budget impact model with time horizon of 5 years	At year 5, the net budget savings were €4.05 to 303.86 million for rituximab and €19 to 172 million for trastuzumab	The cost saving could potentially extend treatment to 291–15,671 more patients with rituximab and 622–3688 more patients with trastuzumab

[a]Includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK
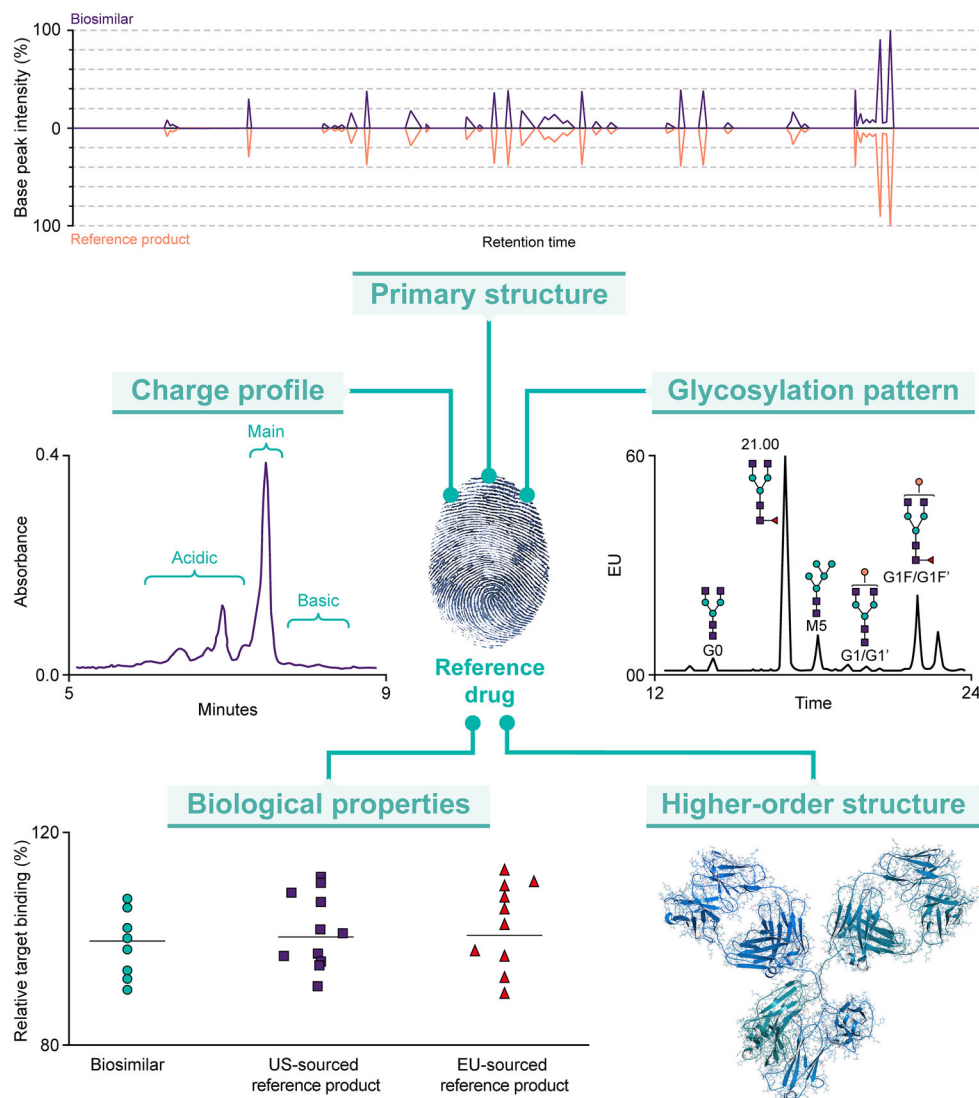
Fig. 2 Methods used to determine the quality attribute "fingerprint" of the biosimilar

The definition of biosimilars applied here excludes molecules that are available in certain regulatory regions outside the EU and USA but were not approved following a stringent regulatory approval process—so-called intended copies or nonregulated biologics [61] (Table 1, Supplementary Material).

Totality of Evidence

For biosimilars the focus for approval is on the totality of evidence generated through a comprehensive and complex comparability exercise using a stepwise approach. The aim is not to re-establish a product's efficacy/safety profile but to demonstrate similarity to the originator product for which a benefit–risk profile has already been established. The first step is to establish similarity in terms of quality (physicochemical and biological), the second is a pharmacological comparison (non-clinical comparability), and the final step is clinical comparability (clinical trials [58]). As shown in Fig. 3 [62], most of the regulatory emphasis with biosimilars is placed on the first (analytical) step or proving that the biosimilar is chemically,
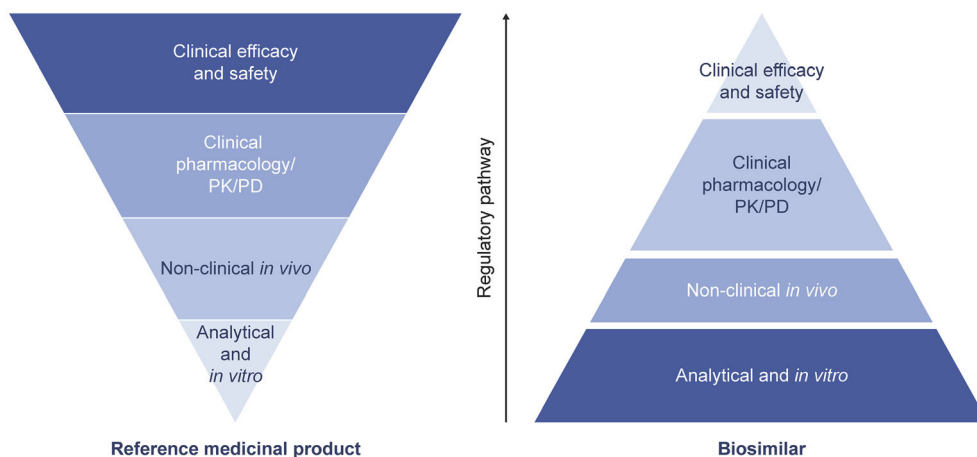
Fig. 3 Comparison of the development pathways for reference biologics and biosimilars(Reproduced from Future Oncol. (2021) 17(19), 2529–2544 with permission of Future Medicine Ltd.) [65]

structurally, and biologically highly similar to the originator molecule. Only if these conditions are met will the biosimilar be taken to the next level of scrutiny in studies involving humans. In most cases, this starts with a determination of the pharmacokinetic (PK) profile. Of note, biosimilar candidate products for the treatment of retinal vascular diseases have not undergone phase I studies because of the limited relevance of systemic pharmacokinetics/ pharmacodynamics resulting from intravitreal administration. For products where accepted pharmacodynamic markers exist, biosimilars may be approved on the basis of combined pharmacokinetic/pharmacodynamic studies, e.g., blood glucose concentrations in clamp studies for insulins, absolute neutrophil counts for granulocyte-colony stimulating factor, or serum calcium levels for teriparatide. However, for many products, including most monoclonal antibodies, such pharmacodynamic markers do not exist and well-designed, adequately powered phase III studies are required to confirm similarity to the reference product in terms of clinical efficacy and safety, usually involving several hundreds of patients [62, 63]. These trials are designed to exclude clinically meaningful differences in efficacy, safety, and immunogenicity and are performed in a patient population that is representative of approved therapeutic indications of the reference product and that will be sensitive for detecting potential differences between the biosimilar and the reference [64]. Typically, an equivalence design with symmetric inferiority and superiority margins is used [53].

As for all biological products, manufacturers of biosimilars are required to provide regulatory authorities with robust post-approval risk management plans and pharmacovigilance programs to identify, characterize, and minimize a medicine's important risks when used in wider patient populations [66].

Immunogenicity

A key consideration when developing any biological drug, including biosimilars, is their potential to elicit the formation of anti-drug antibodies (ADAs), i.e., their immunogenicity. Recent published evidence of rare, but severe, cases of intraocular inflammation after intravitreal injection of brolucizumab have sensitized the ophthalmology community to this topic [67, 68]. Whether a biological elicits ADAs depends on a number of product, patient, and clinical factors [69, 70]. The impact of ADAs can range from having no clinical effect to reducing a drug's effect by interfering with its ability to bind its target, or increase the clearance of the drug from circulation, or in some cases eliciting hypersensitivity reactions [71, 72]. Animal models are not predictive for immunogenic

Table 2 Incidence of immunogenicity in selected phase III trials comparing reference biologics and biosimilars

	Study type	No. of patients	Reference/ biosimilar	Timepoint	Reference	Biosimilar
Rheumatoid arthritis						
Alten et al. [137]	RCT, DB, EQ	650	Infliximab/ PF-06438179	54 weeks	83/143 (58)	146/280 (52)
Smolen et al. [138]	RCT, DB, EQ	584	Infliximab/SB2	54 weeks	170/293 (58)	180/290 (62)
Choe et al. [139]	RCT, DB, EQ	584	Infliximab/SB2	30 weeks	145/292 (50)	158/287 (55)
Fleischmann et al. [140]	RCT, DB, EQ	597	Adalimumab/ PF-06410293	26 weeks	150/299 (50)	131/297 (44)
Cohen et al. [141]	RCT, DB, EQ	645	Adalimumab/ BI 695501	24 weeks	21/321 (7)	11/324 (3)
Weinblatt et al. [142]	RCT, DB, EQ	554	Adalimumab/SB5	24 weeks	87/273 (32)	88/268 (33)
Emery et al. [143]	RCT, DB, EQ	505	Etanercept/SB4	52 weeks	39/296 (13)	3/299 (1)
Suh et al. [144]	RCT, DB, SI	372	Rituximab/CT-P10	48 weeks	EU 7/59 (12)/ USA 13/144 (9)	19/155 (12)
Psoriasis						
Griffiths et al. [145]	RCT, DB, EQ	531	Etanercept/GP2015	50 weeks	0/267 (0)	0/264 (0)
Papp et al. [146]	RCT, DB, EQ	350	Adalimumab/ ABP 501	52 weeks	103/152 (68)	59/79 (75)
Hercogova et al. [147]	RCT, DB, EQ	443	Adalimumab/ MSB11022	52 weeks	195/221 (88)	195/222 (88)
Oncology						
Rezvani et al. [148]	RCT, DB, NI	126	Bevacizumab/ BE1040V	22 weeks	1/44 (2)	1/82 (1)
Reinmuth et al. [149]	RCT, DB, EQ	719	Bevacizumab	12 months	5/358 (1)	5/356 (1)
Waller et al. [150]	RCT, DB, EQ	194	Pegfilgrastim	18 weeks	2/67 (3)	1/125 (1)
Blackwell et al. [151]	RCT, DB, EQ	308	Pegfilgrastim	18 weeks	0/153 (0)	0/155 (0)
Pegram et al. [152]	RCT, DB, EQ	707	Trastuzumab	53 weeks	1/355 (< 1)	1/352 (< 1)

Table 2 continued

	Study type	No. of patients	Reference/ biosimilar	Timepoint	Reference	Biosimilar
Pivot et al. [153]	RCT, DB, EQ	875	Trastuzuamb	27 weeks	0/438 (0)	3/437 (< 1)
Hematology						
Shi et al. [154]	RCT, DB, EQ	407	Rituximab	6 months	1/201 (< 1)	2/206 (1)
Sharman et al. [155]	RCT, DB, EQ	394	Rituximab	12 months	40/198 (20)	43/196 (22)
Nishi et al. [156]	RCT, DB, EQ	334	Darbepoetin alfa	14 weeks	0/163 (0)	0/171 (0)
Endocrinology						
Garg et al. [157]	RCT, OL	597	Insulin aspart/ SAR341402	6 months	107/296 (37)	106/301 (35)
Peterkova et al. [158]	RCT, DB, EQ	147	Growth hormone	12 months	1/49 (2)	3/98 (3)
Czepielewski et al. [159]	RCT, SB	135	Growth hormone	12 months	13/48 (27)	7/49 (14)
Osteoporosis						
Hagino et al. [160]	RCT, SB, EQ	250	Teriparatide/ RGB-10	52 weeks	1/125 (1)	0/125 (0)

DB double blind, *EQ* equivalence trial, *NI* non-inferiority, *OL* open label, *RCT* randomized controlled trial, *SB* single blind, *SI* similarity

responses in humans; therefore potential differences in immunogenicity between a biosimilar and its reference product can only be determined by performing clinical studies. An assessment of comparative immunogenicity is a regulatory expectation in all clinical studies involving biosimilars. Table 2 presents data from various studies comparing biosimilars to their reference products across different therapeutic areas. It should be noted that the sensitivity of ADA assays has greatly increased in the past decade, which means that levels of ADAs reported in more recent studies, including those comparing biosimilars, are often higher than earlier studies involving the same comparators

[73]. As different assays use different methodologies and apply different cutoff limits for positivity, care should be taken when comparing ADA results from different studies. For currently authorized products in the EU and USA across several therapeutic areas, the rate of immunogenicity was found to be similar between biosimilars and their reference products [74].

Extrapolation

Extrapolation refers to the regulatory process of granting a clinical indication that is approved for the reference biologic to a biosimilar

without providing clinical efficacy and safety data from within that indication [75, 76]. Usually, a biosimilar will be tested in a phase III clinical trial involving a study population that is representative of all of the potential approved therapeutic indications of the originator product, but also sensitive for detecting subtle differences (e.g., immunogenicity) that may impact on clinical practice [64]. For example, SB5, a biosimilar version of adalimumab, was approved on the basis of a clinical trial involving patients with RA, as this was the patient population deemed the most sensitive. SB5 was also approved for the other indications approved for the reference product including juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, Crohn's disease (including pediatric), ulcerative colitis, uveitis (including pediatric), and hidradenitis suppurativa [77]. The scientific rationale for extrapolation is based on a demonstration that the reference and biosimilar products have the same mechanism of action [78]. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) state that if the totality of evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, it is possible for the biosimilar manufacturer to use these data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer (FDA, Biosimilar product regulatory review and approval [76]). Scientific justification can be based on existing literature, or by additional in vitro data supporting similarity across indications. Extrapolation is also applied following major changes in the manufacturing process of reference biologicals. The manufacturer follows regulatory guidance to conduct a comprehensive comparability program to establish that any pre- and post-manufacturing changes are sufficiently similar to allow continued authorization [76]. Therefore, currently marketed biologic molecules are, in a way, biosimilars of themselves at the time of their first approval.

Interchangeability

A source of confusion when discussing biosimilars remains around the theme of "interchangeability", which is complicated by different meanings in different jurisdictions. Interchangeability refers to the exchanging of one medicine with another one that is expected to have the same clinical effects owing to high levels of similarity. Switching refers to interchanging an originator or biosimilar for a different biosimilar with the agreement of the prescriber, whereas (automatic) substitution occurs at the level of the pharmacist without consulting the prescriber [79]. In the EU, interchangeability is mostly a scientific term. The EMA does not address interchangeability directly and leaves these decisions to individual member states and automatic substitution of biosimilars is not practised in most EU countries. In the USA "interchangeable" is a legal designation allowing pharmacists to substitute biosimilars (if so permitted by state laws [80]) and it requires additional clinical evidence. In July 2021 the FDA approved the first interchangeable biosimilar product, insulin glargine-yfgn, a biosimilar of insulin glargine [81, 82]. Both biosimilars and interchangeable products have to adhere to the same standards of similarity. The view that biosimilars and originator products will not differ in their clinical effects is supported by published clinical studies and post-marketing surveillance data [79]. Indeed, systematic literature reviews conclude that the current body of evidence suggests no clinically relevant impact of initiating or switching to biosimilars across a number of therapeutic areas [74, 83, 84]. However, interchangeability may impede pharmacovigilance and traceability as not all jurisdictions require innovators and biosimilars to have distinct biological names [85].

THE BIOSIMILARS PIPELINE IN OPHTHALMOLOGY

Several biosimilar candidates of ranibizumab and aflibercept are currently in development and the first biosimilar ranibizumab was

Table 3 Biosimilars to ranibizumab, aflibercept, and bevacizumab in late-stage clinical trials/development

Reference product	Biosimilar	Company	Stage and population	Indication
Ranibizumab	CKD-701 [86]	Chong Kun Dang	Phase III	nAMD
	FYB201[a] [87]	Formycon AG/Bioeq (Coherus)	Submitted to FDA	nAMD
	SB11 [88, 89]	Samsung Bioepis	Approved by the EMA in August and the FDA in September 2021	nAMD
	Xlucane [90]	Xbrane Biopharma	Phase III	nAMD
	GNR-067 [91]	Generium Pharmaceutical	Phase III	nAMD
	LUBT010 [92]	Lupin Ltd	Phase III	nAMD
Aflibercept	ABP-938 [93]	Amgen	Phase III	nAMD
	FYB203 [94]	Formycon AG/Bioeq	Phase III	nAMD
	MYL-1701P/ M710 [95]	Mylan/Momenta Pharmaceuticals	Phase III	DME
	SB15 [96]	Samsung Bioepis	Phase III	nAMD
	SCD-411 [97]	Sam Chun Dang Pharm	Phase III	nAMD
Avastin	ONS-5010 [98]	Outlook Therapeutics	Phase III	nAMD
	HLX04-O [99]	Shanghai Henlius Biotech	Phase III	nAMD

[a]Formerly known as CHS3551

recently approved by the FDA and the EMA (Table 3).

The initial results from the randomized, double-blind, phase III trial of SB11 (Samsung Bioepis, South Korea) in nAMD were recently published [100]. A total of 705 patients with nAMD were randomized 1:1 to receive SB11 or reference ranibizumab (both 0.5 mg Q4W) until week 48 with the last assessment at 52 weeks. Two primary endpoints were defined to satisfy different regulatory agencies: central subfield thickness (CST) at week 4 (EMA endpoint) and best corrected visual acuity (BCVA) at week 8 (FDA/Korean MFDS endpoint). The difference in CST at week 4 was -8.4 (95% CI -19.4 to 2.7) with changes in CST of -108 and -100 μm for SB11 and reference ranibizumab, respectively.

The difference in BCVA at week 8 was -0.8 (90% CI -1.8 to 0.2) with changes in BCVA of $+6.2$ and $+7.0$ letters for SB11 and reference ranibizumab, respectively. SB11 was concluded to be non-inferior to reference ranibizumab for the prespecified primary endpoints. The secondary endpoints of safety, immunogenicity, and pharmacokinetics were similar between SB11 and reference ranibizumab. At week 52 the differences in BCVA (-0.6, 90% CI -2.1 to 0.9) and CST (-14.9, 95% CI -25.3 to -4.5) were maintained, as were other secondary endpoints and safety criteria [101]. On the basis of these data, SB11 was approved by the EMA in August and the FDA in September 2021. Extrapolation of SB11 from nAMD to other indications may not be as contentious as

for biosimilars in other therapeutic areas given that its mechanism of action is determined by binding of VEGFA across all authorized indications, it has generally low immunogenicity [100], is similar to reference ranibizumab with respect to structural, physicochemical, and biological properties [100], and has a non-glycosylated antibody fragment [102]. The European Public Assessment Report (EPAR) from the EMA states that "extrapolation to all approved indications of Lucentis applied for is supported" [103] and so in Europe SB11 is licensed for nAMD, proliferative diabetic retinopathy (DR), DME, macular edema associated with RVO, and choroidal neovascularization. The formulation of SB11 contains the same excipients in the same quantities as the reference product [103]. The FDA approved all indications with the labeled recommended dose of 0.5 mg (0.05 mL) including AMD, RVO and choroidal neovascularization. DR and DME were excluded [88] as the 0.3 mg (0.05 mL) presentation used for DR and DME was not available at the time of approval.

In its phase III trial within the nAMD population (COLUMBUS-AMD, $N = 477$) FYB201 (0.5 mg Q4W) (Formycon AG/Bioeq, Germany) was found to be equivalent to reference ranibizumab (0.5 mg Q4W) with respect to BCVA following 8 weeks of treatment, the primary endpoint. In the US-relevant population (baseline BCVA between 20/32 and 20/100 Snellen equivalent) investigators observed a mean change from baseline BCVA of + 5.1 vs + 5.6 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) test (difference − 0.4, 90% CI − 1.6 to 0.9) for patients treated with FYB201 or reference ranibizumab, respectively, meaning that the two treatments were equivalent. The difference in CST at week 48 was 3.68 μm (90% CI − 13.28 to 20.63 μm) from baseline CST of 182.9 μm and 190.8 μm for FYB201 and reference ranibizumab, respectively. There were no safety or immunogenicity concerns and outcomes did not differ between treatments [104].

PRACTICAL GUIDE FOR THE USE OF BIOSIMILARS

Achieving the full cost-saving benefits of biosimilars requires patients currently receiving the reference product to switch to a biosimilar. The key question for patients and prescribers alike is will switching have any untoward effects such as loss of disease control, increased rates of adverse events, or more pronounced immunogenicity? A large number of studies have provided reassurance that switching from reference biologics to biosimilars is effective and safe [26, 74, 105–111].

In those therapeutic areas where biosimilars have been available for a number of years, it is apparent that the quality of physician–patient communication can have a large impact on the success of a biosimilar switch, and particularly on a phenomenon known as the nocebo effect. The nocebo effect is the opposite to the placebo effect, being defined as "a negative effect of a pharmacological or non-pharmacological medical treatment that is induced by patients' expectations, and that is unrelated to the physiological action of the treatment" [112]. The nocebo effect may come into play when patients are switched from a reference biological to a biosimilar, and may be triggered by perceptions of biosimilars as "cheap copies" of branded medicines. It can have a number of potential consequences including increased symptom burden, psychological distress, and the number of adverse events experienced by patients; non-adherence, reduced quality of life, and wasted medication; increased healthcare costs; more complicated treatment regimens; and the cost savings from biosimilars not being realized [113–117]. The effects of the nocebo effect can be mitigated through physicians having a better understanding of biosimilars including how they are approved and passing this increased confidence onto their patients. In addition, better physician and patient education and communication, finding a balance

between communicating important clinical information and counselling on safety profile expectations, and using educational strategies such as leaflets and patient video clips to recount treatment experiences could help to prevent the nocebo response [118–124]. However, a large systematic review of double-blind versus open-label studies of switching from an originator product to a biosimilar across several therapeutic areas noted that current evidence is insufficient to confirm a biosimilar nocebo effect, although there was some evidence to support the theory [125]. Even though open-label studies did show a decrease in persistence versus clinical trials, this was not associated with a decrease in efficacy [74].

Some physicians may query why they should use biosimilars when payers will reimburse reference products, or when bevacizumab or ziv-aflibercept is available to them. The fact that the use of both bevacizumab and ziv-aflibercept in ophthalmology is off-label, together with concerns regarding inflammation and infection following intravitreal administration of both products, may create a sense of uncertainty with prescribers [39–42, 126]. Furthermore, the use of bevacizumab is not available in all countries, or even uniformly within countries, reflecting diverging opinions of governments and clinical societies on its use [127]. With ziv-aflibercept there are also concerns over potential retinal damage caused by its hyperosmotic solution [38, 126], with its ophthalmic use in the EU being contraindicated for that reason. Finally, while the questioning of the use of biosimilars might be reasonable on an individual level, the reinvestment of savings provided by biosimilars on institutional, regional, and national levels (Table 1) can be used to improve patient care by treating more patients without increasing cost. Other potential benefits of the savings resulting from the use of biosimilars include taking on more staff to increase capacity, or investing in training and education for staff and patients around the subject of biosimilars [22, 51].

CONCLUSIONS

High-quality biosimilars may soon reach the field of ophthalmology and hold the promise of reducing drug expenditures and improving access to high-quality biologics. A growing amount of evidence from clinical trials and real-world studies from multiple therapeutic areas has failed to find clinically relevant differences between biosimilars and their originator products in terms of efficacy, safety, and immunogenicity. Furthermore, the benefits of biosimilars go beyond that of mere cost savings for healthcare systems. The acceptance and use of biosimilars can increase patients' access to biological therapies, increase the number of healthcare providers available to treat patients via redeployment of savings, shift the recommendation of biological therapy earlier in treatment algorithms and guidelines, and fuel innovation in the development of new treatments. All of these will undoubtedly improve outcomes for patients and healthcare systems alike.

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