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Critical appraisal and future outlook on anti-inflammatory biosimilar use in chronic immune-mediated inflammatory diseases

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ABSTRACT

Biosimilars represent a novel category in the world of follow-up medicinal products with the requirement that they are highly similar but not identical to an approved originator biologic medicine, with no clinically meaningful differences in safety, purity, and potency. In this review, we discuss recent pivotal biosimilar developments for anti-inflammatory therapy in rheumatology, gastroenterology, and dermatology, and the influence of biosimilar availability on patients and payers. Finally, we provide our perspective on the evolution of biosimilar use in these indications in the United States (US) and in Europe and on where this evolution in biopharmaceuticals may lead in the future. Although biosimilars are commonly used in the European Union (EU), there will be an inevitable sea change of acceptance by clinicians, patients, payers, and regulators in the US. It is paramount to educate about biosimilarity, highlighting currently available data gathered from other geographies, in addition to gradually providing clinicians and patients with the necessary experience with these agents ultimately restoring competition in the biologics landscape.

Introduction

While patent expiry in chemical molecules allows the introduction of generics, such competition is not possible in the field of biologics because the producing cell lines remain the possession of the original manufacturer and hence, exact copies of such medicinal products cannot be manufactured. Therefore, substantial efforts have been made to define biosimilarity. According to the definition by the US Food and Drug Administration (FDA), a biosimilar is "highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from an existing FDA-approved reference product [RP]" [1]. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the RP, not to independently establish the safety and effectiveness of the proposed product. The European Medicines Agency (EMA) has a similar definition, noting that a biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine') [2]. Biosimilars are approved according to the same standards of pharmaceutical quality, safety, and efficacy that apply to all biological medicines.

To date, there are several anti-inflammatory biosimilars approved for use in patients with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), juvenile idiopathic arthritis (JIA), Crohn's disease (CD), ulcerative colitis (UC), psoriasis (PsO), and psoriatic arthritis (PsA) (Table 1).

These biosimilars have been approved for all indications for which the RPs are approved. Adalimumab biosimilars are available in the EU but not in the US market, where the RP (Humira®) manufacturer maintains certain intellectual property rights that relate to dosing schemes and not the substance itself, prohibiting market entry until 2023 [3].

Globally, there are more than 560 biosimilars to complex proteins in development, with multiple countries having biosimilars pathways, biosimilars in clinical trials, and regions with marketed biosimilars (See

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Table 1
Biosimilars approved in the US and EU, respectively, for therapy of rheumatoid arthritis, axial spondyloarthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, and psoriatic arthritis [3–6]. Trade names are referenced because biosimilars often do not carry a distinguishing international nonproprietary name (INN).

Reference Products Trade Name (INN)	Biosimilars
Humira (adalimumab)	Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Idacio (adalimumab; EU), Imraldi (adalimumab, SB5; EU)
Enbrel* (etanercept)	US: Brenzys (etanercept-ykro, SB4), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro, SB4) EU: Benepali (etanercept, SB4), Erelzi (etanercept), Nepexto (etanercept, YLB113)
Remicade (infliximab)	US: Avsola, Inflectra (infliximab-dyyb, CT-P13), Ixifi (infliximab-qbtx), Renflexis (infliximab-abda, SB2) EU: Remsima/Inflectra (infliximab, CT-P13), Zessly (PF-06438179), Flixabi (infliximab, SB2)
Rituxan (rituximab)	Truxima (rituximab-abbs, CT-P10), Ruxience (rituximab-pvvr), Rixathon (rituximab, EU), Riximyo (rituximab, EU)

* NOTE: Etanercept (Enbrel) has been approved only for rheumatology indications but not Crohn's disease or ulcerative colitis.

Fig. 1) [7].

Given the financial burden, it is imperative to develop a clear understanding of the role of biosimilars in providing access to care for patients with chronic immune-mediated inflammatory diseases.

In this review, we discuss recent pivotal clinical evaluations of biosimilars in rheumatology, gastroenterology, and dermatology. Key biopharmaceuticals in these therapeutic areas that are affected by patent expiry and hence biosimilar development include molecules inhibiting tumor necrosis factor alpha (either as a monoclonal antibody [adalimumab, infliximab] or as a fusion protein [etanercept]. Another molecule is rituximab, which targets B cells and is used in rheumatic indications. Table 1 provides an overview about biosimilars that have been approved in the US and/or EU in these indications. We will also discuss the influence of patients and payers on biosimilar use. Most importantly, we will evaluate how biosimilar use in Europe and the US has evolved over the past several years and provide our perspectives on their use in the future.

Economic issues

Although enormous efforts have been conducted to reduce spending in pharmaceuticals (ie, through introduction and promotion of generic medicinal products), the last decades have seen a steady and exponential rise in spending for specialty pharmaceuticals[8]. Biosimilars to peptides (eg, certain hormones, insulin) are easier to create in comparison with complex molecules like antibodies when patents expire because it is technically possible to generate near-exact copies of molecules with low levels of post-translational modification. However, complex biologics (including monoclonal antibodies) cannot be copied without access to production cell lines. Moreover, the production process itself is not completely stable over extended time periods [9]. The first definitions of biosimilarity were introduced in 1998 in the EU and an initial regulatory pathway was enacted in 2010 in the US [10], fueling the political interest to reduce the price of biopharmaceuticals through opening this market for competition.

Over the past 10 to 15 years, biosimilar use has evolved in Europe and the US. Several biosimilars are approved under guidelines issued by the EMA, Health Canada, and the World Health Organization, with more than 60 biosimilars approved in the EU since 2006, when the first biosimilar came to market. As of 2019, there were over 700 million patient-days of exposure [11], leading the EMA to conclude, "Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity, or frequency of adverse effects between biosimilars and their reference medicines" [12].

The United States

The first biosimilar was approved by the FDA in 2015 (filgrastim-sndz; Zarxio), and 33 biosimilars have been approved since then (11 launched). In 2019, US health plans covered biosimilars as preferred (ie, the plan required patients to try the biosimilar before gaining access to the RP) in only 14% of decisions [13]. The slow biosimilar uptake has

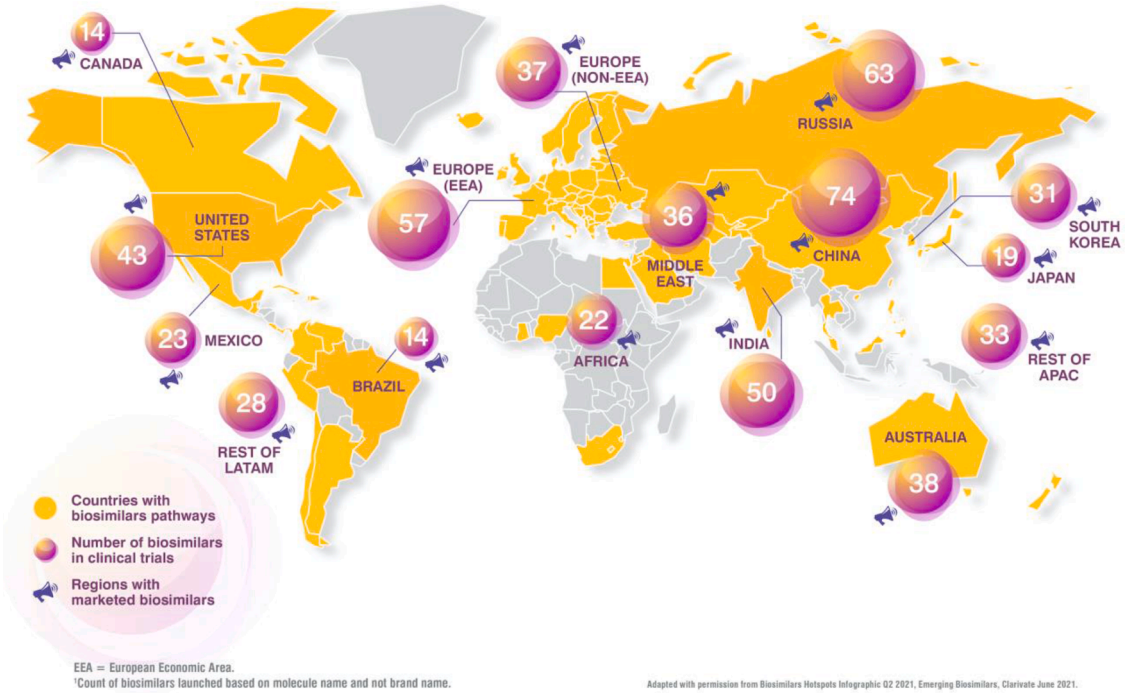

Fig. 1. The global biosimilars landscape [7].

been attributed to factors such as tactics by RP manufacturers to delay biosimilar market entry and patent disputes [14]. Biosimilar use is limited in some healthcare systems due to poor understanding by many providers and patients [15]. The FDA has defined interchangeability as a requirement for mandated switching by pharmacists [1]. Although typical approval studies for anti-inflammatory biosimilars include one or more switches, these do not satisfy regulatory requirements for interchangeability. In July 2021, insulin glargine-yfgn was approved as the first interchangeable biosimilar product after successfully undergoing multiple forward and reverse switch assessments against insulin glargine (Lantus). In October 2021, adalimumab-adbm was approved as the first interchangeable monoclonal antibody (Cyltezo).

In an analysis of a large US commercial health plan covering >14 million people from all 50 states, uptake of biosimilar infliximab was <1%, which may be attributed in part to an early lack of savings in insurer cost or the patient copayment for the biosimilar versus the RP [16]. Current savings are insufficient to promote wider adoption of infliximab biosimilars. Furthermore, savings similar to those achieved in European countries may not be possible unless the US pharmaceutical market undergoes reform.

The European Union

Anti-inflammatory biosimilars, launched in 2006, have been widely adopted, leading to substantial savings and positioning as a main element in the value-based healthcare initiative of the European Commission [17]. In a French economic evaluation, starting treatment with etanercept biosimilars cost less (average lifetime discounted total = €116,912 per patient), with an average of 11,166 quality-adjusted life years (QALY) [18]. Based on an estimated 5122 patients treated with etanercept biosimilar in Germany, a total cost saving of €8.8 million was estimated [19]. A total savings of €21.1 million may be returned to the German healthcare system annually compared with using only the RP, assuming these patients continue to use etanercept biosimilars. The annual cost savings could contribute to providing etanercept biosimilar treatment to an additional 1208 patients.

Methods

As part of this review, a literature search was conducted through August 6, 2021, using the PubMed and Cochrane databases. Search terms included the following: rheumatoid arthritis and biosimilar, axial spondyloarthritis and biosimilar, juvenile idiopathic arthritis and biosimilar, Crohn's and biosimilar, ulcerative colitis and biosimilar, psoriasis and biosimilar, psoriatic arthritis and biosimilar. Articles were selected that described novel and pivotal biosimilar studies. Additional articles were identified using bibliographies, treatment guidelines, and hand searches for the most recent articles citing clinical data of interest. Results were focused on publications in the past year to identify more recent literature.

Results

Clinical observations

Regulatory agencies typically require, as a last step in the approval process, a clinical non-inferiority benchmarking exercise between the originator and biosimilar preparation with regards to pharmacokinetics and efficacy in only one meaningful indication from which the approval is extrapolated into the full breadth of claims established for the original molecule. Prespecified margins for clinical non-inferiority and non-superiority are chosen by regulatory authorities and are typically between 10% and 15% [20]. Interestingly, such pivotal clinical trials are typically conducted in rheumatoid arthritis (RA) and psoriasis but not in inflammatory bowel disease (IBD), which, however, is the most common indication for use of anti-TNF biologicals. This may be motivated by the quality of the clinical activity indices used as a clinical state-of-the-art in the different indications and which may have a higher dynamic range in RA and psoriasis, allowing for better differentiation in active comparator clinical trials.

The clinical approval and positioning process

Regulatory strategies prompt for an approach that is analogous among different biosimilars. Following a thorough molecular characterization, a key clinical comparison is required after which the use is extrapolated to the full spectrum of indication of the RP. The following key examples of clinical experiments from approval studies are highlighted, including additional open-label observations and comparative assessments primarily done for positioning purposes and in an attempt to derive a secondary "biobetter" status through innovations in formulations and use (see Tables 2–4 for an overview of biosimilar clinical trials).

Most approval studies involve double-blind comparisons between a potential biosimilar and the RP that includes induction and maintenance, after which all participants are switched to the biosimilar. An example is the evaluation of the infliximab biosimilar CT-P13. In the PLANETAS study, 221 patients were randomized between CT-P13 and the infliximab RP, receiving the standard dose (5 mg/kg bodyweight) approved for axSpA to demonstrate equivalence for 30 weeks [75], whereas the PLANETRA study showed equivalence within the specified noninferiority margin of 15% at the week 30 endpoint in 606 patients with RA using the approved dose (3 mg/kg bodyweight) [76]. After 30 weeks, all patients transitioned to CT-P13.

Further examples include development of the etanercept biosimilar YLB113, where a randomized, double-blind comparison was conducted in 528 patients with RA at week 24 [36].

FKB327 is an adalimumab biosimilar that was evaluated in a randomized, double-blind study followed by an open-label extension of 728 patients with RA, which demonstrated comparable efficacy and immunogenicity characteristics at week 24, after which they were re-randomized 2:1, remaining on the same study drug or switching to the other up to week 54 in an open-label extension over a total of 104 weeks [25]. Neither efficacy nor immunogenicity was impacted by switching or double switching between treatments [25].

The adalimumab biosimilar GP2017 was compared against the RP in 465 patients with PsO [51]. After examination of equivalence based on the PASI75 at week 16, patients were rerandomized to switch or continue (2:1) without any differentiation between the two products. The approval of rituximab biosimilars is more complex because separate studies were needed to demonstrate equivalence in chronic inflammatory and hematological conditions. Typically, these were conducted in RA and B-cell–driven hematologic malignancies [43–46].

Some biosimilars have undergone additional studies in key indications for use. These are not required for regulatory approval, which includes already the extrapolation beyond the disease in which similarity has been established. NOR-SWITCH, sponsored by the Norwegian government, was a randomized, non-inferiority, double-blind, phase 4 trial where 482 patients on stable treatment with reference infliximab (>6 months) from different indications (axSpA, CD, plaque PsO, PsA, RA, UC) were randomized 1:1 for switching to the infliximab biosimilar CT-P13 or continuation of the RP [38]. The primary endpoint was disease worsening (defined for each indication) over 52 weeks. Although the study demonstrated non-inferiority in a real-world population within a two-sided margin of 15%, it also demonstrated that many patients under stable infliximab treatment were not in remission while receiving long-term therapy.

Recently another phase 3, non-inferiority, double-blind study evaluating CT-P13 against the RP was conducted in biologic-naive patients with CD, with a primary endpoint at week 30, after which all patients were continued on CT-P13 [71]. No differences in efficacy, safety, or immunogenicity were reported. The patient population, which is considered more similar to the real world than that in the original

Table 2
Selected publications of clinical studies evaluating biosimilars for the therapy of rheumatologic diseases in 2020 [21–46].

Biosimilar	Disease state(s)	Study	N	Study Type	Study Duration	Primary End Point	Limitations
ABP 501 (adalimumab; Humira)	RA	Cohen et al., 2019 [21]	467	Open-label extension study	72 weeks	Safety	Open-label, single-arm study design; bias introduced via patient drop-out over time
BI 695501 (adalimumab; Humira)	RA	Cohen S et al., 2019 [22]	430	Open-label extension study	2 years	Investigator-assessed drug-related AEs	Open-label, non-randomized design; entrance based on self-selection
CinnoRA (adalimumab; Humira)	Healthy volunteers	Jamshidi et al., 2020 [23]	74	Randomized, double-blind	71 days	AUC	Included 78% male patients
CT-P17 (adalimumab; Humira)	RA	Kay et al., 2021 [24]	648	Randomized, double-blind	24 weeks	ACR20	Short follow-up, no comprehensive PK data
FKB327 (adalimumab; Humira)	RA	Alten et al., 2020 [25]	728	Open-label extension	80 weeks (104 weeks from start of double-blind study)	Immunogenicity and safety	Potential for patient selection bias
GP-2017 (adalimumab; Humira)	RA	Wiland et al., 2020 [26]	353	Randomized, double-blind	48 weeks	DAS28-CRP	Study was not designed to assess the effect of treatment switching
SB5 (adalimumab; Humira)	RA, axSpA, JIA	Bruni et al., 2021 [27]	82	Real world	6 months	Patient's global assessment	Lack of sample size calculation and the need for corroboration by results from large-scale initiatives
SB5 (adalimumab; Humira)	RA	Weinblatt et al., 2018 [28]	542	Randomized, phase 3	52 weeks	ACR20/50/70	Study was not designed for statistical comparisons of equivalence
rhTNGR:Fc (etanercept)	RA	Wu et al., 2020 [29]	89	Randomized, open-label	52 weeks	mTSS change from baseline	Open-label study design; insufficient power to detect differences between treatment groups
SB4 (etanercept; Enbrel)	RA, axSpA	Al Tabaa et al., 2020 [30]	183	Real world	6 months	Switch rate; discontinuation rate	Real-world study; physician selection bias
SB4 (etanercept; Enbrel)	RA, axSpA	Felis-Giemza et al., 2019 [31]	168	Observational	6 months	Treatment discontinuation	Disease activity at switch differed among patients
SB4 (etanercept; Enbrel)	RA, axSpA	Glintborg et al., 2020 [32]	4719	Registry study; observational cohort	6 months	Hepatobiliary events	Potential for coding errors/ lack of consistency
SB4 (etanercept; Enbrel)	RA, axSpA	Selmi et al., 2020 [33]	358 (RA); 199 (axSpA)	Real world	6 months	DAS28 or BASDAI	Patient selection bias
SB4 (etanercept; Enbrel)	RA, axSpA	Tweehuysen et al., 2020 [34]	625 (SB4) 600 (etanercept)	Open-label cohort	6 months	Treatment persistence	Inability to conclude that the communication strategy of treatment switching had a direct effect on SB4 acceptance and persistence rates
YLB113 (etanercept; Enbrel)	Healthy subjects	Shennak et al., 2020 [35]	52	Randomized, open-label, crossover	72 days	Maximum serum concentration	Significant period effect
YLB113 (etanercept; Enbrel)	RA	Yamanaka et al., 2020 [36]	528	Randomized	56 weeks	ACR20 response rate at week 24	Small sample size; small differences in product formulation and syringe coating
Infliximab	RA, axSpA	Convertino et al., 2020 [37]	606 and 434	Real world	3 years	Persistence	Potential physician bias
CT-P13 (infliximab; Remicade)	axSpA, RA	Jørgensen et al., 2017 [38]	482	Randomized, noninferiority, double-blind	52 weeks	Disease worsening during 52-week follow-up	The study was not powered to demonstrate noninferiority in each individual disease subgroup
CT-P13 (infliximab; Remicade)	RA, axSpA	Kim, Lee, et al., 2020 [39]	491	Retrospective	Up to 5 years	Long-term safety	Potential for data recording errors or missing information
CT-P13 (infliximab; Remicade)	RA	Westhovens et al., 2021 [40]	357	Randomized, double-blind	64 weeks	DAS28-CRO response at week 22	Limited follow-up; exclusion of patients with BMI ≥35
PF-06438179/ GP1111 (infliximab; Remicade)	RA	Cohen et al., 2020 [41]	650	Double-blind, active-controlled	78 weeks	ACR20 response	Lack of control group of patients maintained on reference infliximab from the EU
PF-06438179/ GP1111 (infliximab; Remicade)	RA	Kameda et al., 2020 [42]	650	Randomized, double-blind	30 weeks	ACR20 response rate	Subgroup analyses were created post hoc

(*continued on next page*)

Table 2 (*continued*)

Biosimilar	Disease state(s)	Study	N	Study Type	Study Duration	Primary End Point	Limitations
ABP 798 (rituximab; Rituxan; MabThera)	RA	Burmester Chien et al., 2020 [43]	311	Randomized, double-blind	52 weeks	Area under the serum concentration-time curve	Conducted in patients with RA
ABP 798 (rituximab; Rituxan; MabThera)	RA	Burmester Drescher et al., 2020 [44]	311	Randomized, double-blind	24 weeks	DAS28-CRP change from baseline at week 24	Lack of inclusion of DAS28-ESR measurements; lack of long-term follow-up
DRL_RI (rituximab; Rituxan; MabThera)	RA	Haridas et al., 2020 [45]	276	Randomized, double-blind	24-week treatment period; follow-up through week 52	$AUC_{0–14\ days}$; $AUC_{0–14\ days,}$ first infusion; $AUC_{0-\infty}$; $AUC_{0-\infty,}$ entire course; $AUC_{0-t,}$ second infusion	Study population differs from the labeled population; not statistically powered to detect efficacy similarity
GP2013; Rixathon (rituximab; Rituxan; MabThera)	RA	Smolen et al., 2020 [46]	312	Randomized	52 weeks	DAS28 at week 24	Potential bias following patient dropout

RA, rheumatoid arthritis; axSpA, axial spondyloarthritis, JIA, juvenile idiopathic arthritis.

Table 3
Selected publications of clinical studies evaluating biosimilars for the therapy of psoriasis and psoriatic arthritis until 2021 [27,31,32,34,37,38,47-55].

Biosimilar	Disease State(s)	Study	N	Study Type	Study Duration	Primary End Point	Limitations
adalimumab; Humira	PsO	Loft et al., 2021 [47]	348	Cohort, switch	1 year	Drug retention at 1 year	Only Danish patients included; individual adalimumab biosimilars not assessed
BI 695501 (adalimumab; Humira)	PsA, PsO	Menter et al., 2021 [48]	317	Randomized, double-blind	24 weeks	Proportion of patients with ≥75% reduction in PASI 75 at week 16	Relatively short treatment period
BI 695501 (adalimumab; Humira)	PsA, PsO	Boehringer Ingelheim, 2021 [49]	238	Randomized, switching	58 weeks	Area under the plasma concentration time curve, Week 30 to 32	Full results not published
Exemptia (adalimumab; Humira)	PsA, PsO	Khandpur et al., 2020 [50]	16	Prospective pilot case series	20 weeks	DAPSA 20 and PASI 50 scores at week 12	Small sample size; lack of comparator
GP2017 (adalimumab; Humira)	PsO	Blauvelt et al., 2018 [51]	465	Randomized, double-blind	51 weeks	PASI 75 at week 16	Not powered to assess treatment switching
MSB11022 (adalimumab; Humira)	PsO	Hercogová et al., 2020 [52]	443	Randomized, double-blind	66 weeks	PASI 75 at week 16	Not powered for statistical comparisons of equivalence after switching
SB5 (adalimumab; Humira)	PsA	Bruni et al., 2021 [27]	82	Real world	6 months	Patient's global assessment	Lack of sample size calculation and the need for corroboration by results from large-scale initiatives
SB5 (adalimumab; Humira)	PsA, PsO	Di Cesare et al., 2020 [53]	23	Prospective, switching	24 weeks	PASI, BASDAI	Small sample size
SB4 (etanercept; Enbrel)	PsA	Bonifati et al., 2020 [54]	87	Open-label	1 year	Proportion of subjects maintaining a cDAPSA ≤13 after 1 year from switching	Small sample size; open-label nature
SB4 (etanercept; Enbrel)	PsO	Egeberg et al., 2020 [55]	189	Real world	2.5 years	PASI, DLQI	No data on other biologics for comparison
SB4 (etanercept; Enbrel)	PsA	Felis-Giemza et al., 2019 [31]	168	Observational	6 months	Treatment discontinuation	Disease activity at switch differed among patients
SB4 (etanercept; Enbrel)	PsA	Glintborg et al., 2020 [32]	4719	Registry study; observational cohort	6 months	Hepatobiliary events	Potential for coding errors/lack of consistency
SB4 (etanercept; Enbrel)	PsA	Tweehuysen et al., 2020 [34]	625 (SB4) 600 (etanercept)	Open-label cohort	6 months	Treatment persistence	Inability to conclude that the communication strategy of treatment switching had a direct effect on SB4 acceptance and persistence rates
Infliximab	PsA, PsO	Convertino et al., 2020 [37]	606 and 434	Real world	3 years	Persistence	Potential physician bias
CT-P13 (infliximab; Remicade)	PsA, PsO	Jørgensen et al., 2017 [38]	482	Randomized, noninferiority, double-blind	52 weeks	Disease worsening during 52-week follow-up	The study was not powered to demonstrate noninferiority in each individual disease subgroup

PsA, psoriatic arthritis; PsO, psoriasis.

Table 4
Selected publications of clinical studies evaluating biosimilars for the therapy of Crohn's disease/ulcerative colitis until 2021 [37,38,56-74].

Biosimilar	Disease State(s)	Study	N	Study Type	Study Duration	Primary End Point	Limitations
ABP 501 and SB5 (adalimumab; Humira)	CD, UC	Barberio et al., 2021 [56]	156	Multicenter cohort	40 weeks	Clinical benefit	Limited sample size; relatively short follow-up; heterogeneous population
ABP 501 (adalimumab; Humira)	CD	Ribaldone et al., 2020 [57]	87	Observational	6 months	Clinical response at 12 weeks; drug retention at 24 weeks	Relatively small sample size; observational design; ABP501 was not directly compared with the RP
BI 695501 (adalimumab; Humira)	CD	Hanauer et al., 2021 [58]	147	Randomized, double-blind, switch	56 weeks	CDAI decrease ≥70 points at 4 weeks	Double-blind first 24 weeks only
Exemptia (adalimumab; Humira)	UC	Chandra et al., 2019 [59]	25	Retrospective, real-life study	24 weeks	Clinical remission	Small sample size; retrospective nature
SB5 (adalimumab; Humira)	CD, UC	Derikx et al., 2021 [60]	481	Retrospective, observational cohort	13.7/8.3 months (median follow-up in switch/start cohort)	Drug persistence	Lack of a control arm; some follow-up data were lacking
SB5 (adalimumab; Humira)	CD, UC	Lukas et al., 2020 [61]	186	Retrospective	10 weeks	Disease activity (Harvey-Bradshaw index; partial Mayo score)	Short follow-up period; lack of patient randomization before the switch
SB5 (adalimumab; Humira)	CD	Ribaldone et al., 2021 [62]	61	Observational, switch	6 months	Success of the switch to SB5	Relatively small sample size; lack of endoscopic outcome
Infliximab	CD, UC	Convertino et al., 2020 [37]	606 and 434	Real world	3 years	Persistence	Potential physician bias
Infliximab biosimilar	CD, UC	Nikkonen et al., 2020 [63]	51	Real world	1 year	Therapy outcomes	Small sample size; retrospective nature
CT-P13 (infliximab; Remicade)	CD, UC	Barberio et al., 2020 [64]	184	Retrospective, real world	52 weeks	Clinical response	Heterogeneity of the population; limited sample size; retrospective nature
CT-P13/SB2 (infliximab; Remicade)	CD, UC	Hanzel et al., 2021 [65]	176	Multicenter, prospective cohort, switch	12 months	Clinical remission per physician's assessment without concomitant steroid therapy 12 months since index switch	Observational nature
CT-P13 (infliximab; Remicade)	CD, UC	Ilias et al., 2019 [66]	174	Prospective, observational study	24 weeks	Clinical remission	Observational nature; lack of long-term follow-up
CT-P13 (infliximab; Remicade)	CD, UC	Jørgensen et al., 2017 [38]	482	Randomized, noninferiority, double-blind	52 weeks	Disease worsening during 52-week follow-up	The study was not powered to demonstrate noninferiority in each individual disease subgroup
CT-P13 (infliximab; Remicade)	CD	Meyer et al., 2018 [67]	5050	Comparative equivalence cohort	28 months	A composite end point of death, CD-related surgery, all-cause hospitalization, and reimbursement of another biologic therapy	Inclusion of only infliximab-naive patients; the use of an algorithm to identify patients with Crohn's; lack of all relevant clinical data in database
CT-P13 (infliximab; Remicade)	UC	Ollech et al., 2020 [68]	21	Retrospective cohort study	6 months	Colectomy-free survival	Small sample size; retrospective nature
CT-P13 (infliximab; Remicade)	CD, UC	Petitdidier et al., 2020 [69]	364	Real world	54 weeks	Disease activity	Retrospective nature; absence of standardization of therapeutic drug monitoring and endoscopic assessment
CT-P13 (infliximab; Remicade)	CD, UC	Schreiber et al., 2021 [70]	131	Randomized, multicenter, open-label	54 weeks	Observed predose CT-P13 concentration at week 22	Open-label study design; small sample size
CT-P13 (infliximab; Remicade)	CD	Ye et al., 2019 [71]	220	Randomized, double-blind, multicenter	54 weeks	CDAI-70 response at week 6	Lack of statistical power limits interpretation of week 54 data
Inflectra/CT-P13 (infliximab; Remicade)	CD	Kósa et al., 2020 [72]	476 and 397	Real-world administrative database study	6-year time window (3 years before and after start of treatment)	Dose escalation	Retrospective nature; change in reimbursement policy
SB2 (infliximab; Remicade)	CD, UC	Macaluso et al., 2020 [73]	276	Observational	8 months (median follow-up)	Safety	Small sample size; indirect comparisons; lack of data on endoscopic response, drug serum levels, and antidrug antibodies
SB2 (infliximab; Remicade)	CD, UC	Massimi et al., 2021[74]	85	Multicenter, prospective, switch	329 days after switching (mean follow-up)	Clinical activity	Limited sample size; relatively short follow-up; heterogeneous baseline population

CD, Crohn's disease; UC, ulcerative colitis.

placebo-controlled registration trials of the RP, showed high clinical remission and endoscopic improvement rates. A prospective study of switching between biosimilars was also conducted in IBD, in which 176 patients with either CD or UC underwent 2 switches (infliximab RP to CT-P13 to SB2; group 1), one switch from CT-P13 to SB2 (group 2), or one switch from infliximab to CT-P13 (group 3), without differences in clinical remission or treatment persistence after 12 months [65].

A recent innovation was the evolution of subcutaneous infliximab. It is not anticipated that the biosimilarity paradigm results in technical innovation because improved performance of a biosimilar molecule than the RP precludes approval. Here, a formulation innovation transitioning from intravenous to subcutaneous administration was evaluated. It is surprising that the original manufacturer missed out on this important aspect of development. Two multicenter, randomized trials conducted in RA and in a mixed population of patients with CD and UC demonstrated that use of subcutaneous infliximab every 2 weeks starting at week 6 leads to similar pharmacokinetic exposure (area under the curve) and clinical results as with regular intravenous use every 8 weeks [40,70]. Most interestingly, the intravenous induction followed by subcutaneous maintenance might lead to reduced immunogenicity in the sense of a high-zone tolerance induction. The FDA declined to consider approval of the subcutaneous formulation of infliximab as a biosimilar and required submission of a complete biological license application for approval. Two parallel withdrawal studies in the indications of ulcerative colitis and Crohn's disease, respectively, have been conducted (NCT04205643, NCT03945019). It remains to be seen whether this will satisfy regulatory requirements, although vedolizumab was approved using a similar strategy.

Changes in a future regulatory environment

The FDA's Biosimilars Action Plan was published in 2018 to aid the development of the biosimilars market to increase competition for biologic drugs [77,78]. This competition was expected to substantially impact the pharmaceutical industry and national health systems. In 2018, the FDA commissioner, Scott Gottlieb, noted that new policies were aimed toward stimulating biosimilar development and decreasing manufacturing variance of currently available biologics, which will make it easier to copy those drugs in smaller studies [79].

Through May 2021, there were 79 marketing authorization applications for biosimilar products authorized by the EMA [80]. According to the EMA, the guiding principle of a biosimilar development program is to demonstrate similarity between the biosimilar and the RP, ensuring that the previously proven safety and efficacy of the RP also applies to the biosimilar [81]. The clinical efficacy trial, which was required until recently in complex biosimilars, is now being increasingly questioned. Based on a thorough review of biosimilar applications in the EU, in-depth knowledge of the RP allied with high-performing analytical tools largely predicts clinical comparability, subject to confirmation by a comparative pharmacokinetic trial. This represents a shift in attitude toward regulatory approval of biosimilars by the EMA [82].

Indeed, following a completed stakeholder consultation, the Medicines and Healthcare Products Regulatory Agency (MHRA) published a guidance on May 6, 2021, for a streamlined United Kingdom regulatory pathway and requirements for biosimilar licensing [83]. In essence, this guidance removed the requirement for a comparative phase 3 efficacy trial in most cases where a well-argued justification can be provided. This highlights the significant regulatory experience and confidence in the science around characterization of biosimilars based on analytical and functional data, thus translating the learnings and principles relating to regulating manufacturing changes into effective regulation of new biosimilars characterized to have no meaningful clinical difference in quality, efficacy, or safety to the RP in robust comparability studies.

Changes in formularies

European hospitals have largely adopted biosimilars into their formularies, leading to steep price reductions of 10% to 35% or more [84]. Savings totaling €1.6 billion/year may be reached if a 20% price reduction occurs on five off-patent biosimilars [85], which may ultimately contribute to increased clinical guideline compliance [86,87]. NHS England is aiming for 90% of new patients to be prescribed the best-value biological medicine within 3 months of the launch of a biosimilar and actively encourages switching to meet the goal of an 80% biosimilar prescription rate within 1 year [88,89]. The use of gain-sharing agreements, in which commissioners and providers share part of the savings, creates an incentive for the adoption of biosimilars. Cumulative savings related to infliximab are estimated at US $275 million. An interesting further principle is the introduction of quota systems in several European countries in which the prescribing physicians are commanded to use up to 90% biosimilars for certain therapies. This system is not without dispute because it neutralizes the competitiveness in the market in favor of the biosimilar industry.

Further formulary changes are delayed in the US due to patent issues protecting etanercept until 2029 and originator adalimumab at least until 2023. Many states have reduced the ability of pharmacists to automatically substitute for biosimilars without the knowledge of the prescribing HCP.

Acceptance by patients and payers

Disparagement and misinformation about biosimilars may cause patients to fear that they will receive a product that is ineffective, inferior, or unsafe. Patients might request not to receive a biosimilar drug, or if they do receive a biosimilar, they may experience poor clinical outcomes due to a negative preconceived opinion (the "nocebo effect")[90,91].

In a survey of 470 European physicians, 24% thought it was critically important to have sole authority for determining, together with the patient, the appropriate biological medicine; 48% thought it was very important and 23%, somewhat important [92]. A similar pattern was observed regarding the importance of "dispense as written" or "do not substitute." Notably, 62% of physicians did not consider acceptable that pharmacists can decide which product (RP or biosimilar) to dispense.

Opinions have changed over time with education. A French survey of 629 rheumatology patients highlighted the lack of information they had about biosimilars [93]. Among these patients, 43% knew what a biosimilar drug was. Although 47% approved the principle of reducing health costs, only 21% were not hesitant to switch to a biosimilar for potential cost-saving purposes; this reluctance may be partially due to 30% assuming that a less expensive drug is of lower quality [47]. An international survey of 3198 individuals, including patients, caregivers, and the general population, highlighted a lack of information regarding biosimilars [94]. Of the US patients, 47% were using biologics and 11% were using biosimilars, whereas 40% in the EU were using biologics and 27% were using biosimilars. Among these individuals, awareness was significantly higher among patients, patients participating in support groups, and caregivers compared with the general population (45%–78% vs 27%; $P < 0.05$) [94]. Only 6% of the general population reported having a general idea regarding biosimilars.

Under the Alberta Biosimilar Initiative, adult patients (except pregnant women) currently on an RP for which there is a biosimilar version were required to switch to the biosimilar prior to the switch date (January 15, 2021) in order to maintain coverage through their Alberta government-sponsored drug plan [95]. Switching from RPs to biosimilars is projected to save up to $380 million over the next 4 years.

In Germany, the biosimilar uptake rate is among the world's highest (in part, due to a rigid quota system mentioned above), and cost savings of approximately $400 million were reported between 2007 and 2014 [96]. Physician associations negotiate contracts and set budgets to

control health expenditure growth, and biosimilar quotas are monitored at the physician level. The ability of this cost-control measure to increase the biosimilar share is dependent on the particular biologic, the specialty of the physician, and whether the physician prescribes biosimilars regularly [96].

Conclusions

Until now, benchmarking of biosimilar efficacy through clinical trials in key indications in line with regulatory requirements has not led to surprising failures at this stage. It appears that an in-depth understanding of the biochemical, molecular, and pharmaceutical characteristics is creating a high level of confidence and predictability that will lead to a relaxation in the requirement of clinical trials for biosimilar approval. Over the past 5 years, physicians in the EU have embraced biosimilar use at competitive prices to benefit payers and patients. In the US it is expected that this process takes much longer as the introduction of biosimilars was delayed (ie, 2006 in the EU and 2016 in the US) and patents are in force longer to protect use of originators. The increasing acceptance of biosimilars for chronic inflammatory disease therapy will enhance uptake of biosimilars representing novel molecule classes, including vedolizumab and ustekinumab, where patents expire in the very near future in the European region and a few years later in the US. This is important support for diseases that require biologics for potentially life-long therapy with ever-increasing prices for new medicines, where the high level of drug spending otherwise potentially threatens the sustainability of healthcare systems and might lead to rationing. Reducing costs for healthcare provisions with similar health benefits to patients is a cornerstone to value-based healthcare, as laid out by the European commission [17]. Key stakeholders are continually monitoring biosimilar developments, including both supply- and demand-side initiatives, and encouraging countries to learn from each other to enhance their uptake. This is critical for health authorities, particularly as disruptive tactics are initiated (with hurdles such as concealed rebates, prescribing incentives, and other strategies on reference biologics) aimed at limiting biosimilar market entry.

A sustainable biosimilar market that can result from policies designed to eliminate barriers to entry, adoption, and utilization is important. A collaboration among policymakers, patients, and physicians is required to define this framework. Policies such as quotas or prescribing incentives could emerge as a way to encourage uptake, with reimbursement tied to the fulfillment of preset quotas regarding initiation of treatments and biosimilar market share by specialties or indications. Such policies that would provide affordable and accessible therapeutics to patients should be encouraged, despite the seemingly little political appetite to implement them. Encouraging increased competition in the biologics market through biosimilar adoption remains the most promising approach to increase access to much-needed drugs.

The adoption of biosimilars can enhance access to novel therapies. An important factor is the reduction of biopharmaceutical spending in the indication to make space for new, high-priced innovations. Clinical studies examining biosimilars have deepened our understanding of response and non-response, which is the foundation to design sequential therapies from biosimilars to novel mechanisms of action.

The competition among biosimilars and between biosimilars and RPs drives technical innovation. A key example is the creation of a subcutaneous dosing paradigm for infliximab, but there are also numerous improvements in the understanding of pharmacokinetics and algorithms for best individual use. It is important to realize that in the previous setting of a limited number of anti-TNF biologicals with no more than two to three manufacturers, the key market principles ensuring efficiency of economy were defunctionalized, and important improvements in anti-TNF use were not explored despite sufficient profits and large unmet needs of patients. This example may serve as a paradigm prompting discussion to regulate the pharmaceutical industry in greater depth and apply anti-trust principles, which could include the promotion of forced licenses and quicker biosimilar approval. A further example of a lack of competitive research includes the standstill in development of therapeutic endpoints used in industry-driven trials in immune-mediated diseases. These have remained unchanged over time, although remaining unmet needs of patients are large and poorly described. Better therapeutic (symptom-driven scores [eg, fatigue]) and combined endpoints (eg, disease control) allow trials to examine individual, patient-centered optimization strategies of drug use for reduced patient suffering. It also remains unclear whether attenuation, which is frequently observed after successful induction with anti-TNF therapies, is due to mechanism escape, immunization, and hence, neutralization of the biological agent or whether the primary molecular architecture of disease explains these long-term failures. A first step would be a thorough examination as to whether the successfully treated subpopulations overlap between different biological drug classes or whether different mechanisms address complementary subpopulations. Although algorithm studies have been demanded in which either sequential or additive combinations of biologics, including crossovers, are investigated, little interest has been shown by RP manufacturers to explore this route of patient management. Currently, only a few fully powered, randomized, blinded, head-to-head studies have been reported. Biosimilars may change this situation in the near future, as biosimilar manufacturers will be able to offer several mechanisms of action within one company (eg, anti-TNF, anti-integrin (vedolizumab), and anti–IL-12/23 (ustekinumab) for IBD and psoriasis) in Europe as soon as 2024/2025 [97], prompting an interest to study the interactions of these agents in combination or in sequence. However, several issues remain unsolved, which include interactions between agents if these are combined, whether given in parallel or in overlapping sequence, where toxicities could be additive or supra-additive. With new drug classes being approved, such sequencing/combination studies will be driven by the competitive interest to maintain patients on a biosimilars portfolio as long as possible before they proceed to consecutive approaches involving new drug classes.

With more real-world evidence, physicians will become confident not only in initiating patients to biosimilars but also in switching patients to and between them. Although the initial stance toward biosimilars was understandably cautious and conservative in the interests of patients' safety, the analytical and scientific progress and accumulated experience with biosimilars continue to reshape regulatory requirements, generally leading to a reduced burden on clinical studies required for biosimilar regulatory approval. This trend is expected to continue by increasingly employing pharmacodynamic endpoints and biomarkers, but much work remains to make this happen, especially for complex molecules with complex mechanisms of action. The EU biosimilar regulatory framework is robust and able to adapt to advancing knowledge and experience and to strike a balance between regulatory standards, patient safety, and feasibility of biosimilar development.

Future therapeutic paradigms may include biological therapy combinations. A growing area of interest in rheumatology is not only biologics combinations, but combinations with targeted synthetic disease-modifying drugs (tsDMARDs), a designation used for newer, more targeted oral medications, including JAK inhibitors or apremilast, to distinguish them from conventional synthetic DMARDs (csDMARDs), such as methotrexate, sulfasalazine, etc. We have a growing anecdotal literature (mostly from registries) about such combinations. Given cost considerations, a biosimilar landscape may be increasingly important to allow these paradigms to evolve and become implemented in clinical practice.

In the next 5–10 years, after patent expiry, private and public payers will likely demand broader use of biosimilars because biosimilars will become available for an increasing number of therapeutics with different mechanisms of action. Therefore, safety-bound arguments evoking avoidance of side effects will no longer allow first-line use of innovator drugs based only on safety data from pivotal clinical trial

programs. Countries will move at different rates toward acceptance. Increased acceptance of biosimilars by healthcare systems, healthcare professionals, and patients will be a key factor in the uptake of these therapies, but regulatory agencies' variations in biosimilarity designations and pertinent approval pathways could confuse and reduce confidence in the quality, efficacy, and reliability of these agents.

A further task ahead that needs stimulation is to produce data examining the interaction between biosimilars and the subsequent use of novel originators. While the pharmaceutical industry has long focused on "first-line" use for novel drugs, clinical development strategies may have to accommodate the first-line use of biosimilar principles, which are then applied in combination or followed by new therapies that are coming.

Availability and use of biosimilars already impact clinical outcomes in rheumatology, gastroenterology, and dermatology. With biosimilarity opening affordable entry pathways into biologics use, such drugs will be used earlier in the course of disease and will have a beneficial impact on long-term outcome.

Author contributions

All authors made substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data and were fully responsible for drafting the work or revising it critically for important intellectual content. All authors had full access to all the data in the study (as far as applying) and take responsibility for the integrity of the data and the accuracy of the data representation and analysis. The authors made all content and editorial decisions, had final approval of the manuscript, and accept responsibility to submit for publication. **Stefan Schreiber:** Data verification, Conceptualization, Funding acquisition, Investigation, Methodology, Writing - original draft preparation, Writing – Reviewing and Editing. **Luis Puig:** Conceptualization, Supervision, Writing - original draft preparation, Writing – Reviewing and Editing. **João Gonçalves:** Investigation, Methodology, Supervision, Writing - original draft preparation, Writing – Reviewing and Editing. **Philip Mease:** Conceptualization, Writing - original draft preparation, Writing – Reviewing and Editing. **Remo Panaccione:** Conceptualization, Investigation, Supervision, Validation and Visualization, Writing - original draft preparation, Writing – Reviewing and Editing. **Paul Emery:** Data verification, Conceptualization, Writing - original draft preparation, Writing – Reviewing and Editing.

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