

Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician

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Abstract

Purpose of Review Biosimilars of the reference biologic therapeutics infliximab, etanercept, adalimumab, and rituximab are entering the market. Clinical and real-world data on the effects of reference → biosimilar switching are limited. This review was carried out to assess the current body of switching data.

Recent Findings Fifty-three switching studies were identified. Infliximab publications covered CT-P13 (25 studies), SB2 (1), infliximab NK (1), and unspecified infliximab biosimilars (2). Etanercept publications covered SB4 (2) and GP2015 (2). Adalimumab publications covered ABP 501 (2) and SB5 (1). Rituximab publications covered CT-P10 (1). Efficacy

and safety data generally showed no differences between patients who switched treatments versus those who did not. No differences were seen pre- and post-switch. Immunogenicity data were presented in 19/37 (51%) studies.

Summary Additional data from switching studies of these therapies are still required, as is continuing pharmacovigilance. Switching should remain a case-by-case clinical decision made by the physician and patient on an individual basis supported by scientific evidence.

Keywords Biologics · Biosimilars · Switching · Clinical trials · Real world data

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Introduction

Biosimilars are biologic products assessed by regulatory agencies to be similar to a licensed reference product in terms of quality, safety, and efficacy. Different agencies have their own definitions of biosimilarity [1–3], and regional regulatory requirements for biosimilars have been discussed elsewhere [4]. Proposed biosimilar products include both candidate biosimilars (copies of licensed reference products still in development) and intended copies (products marketed without first undergoing rigorous comparative evaluations) [5]. The development of proposed biosimilar products has increased as reference drugs lose patent exclusivity, with the anticipated effect of increasing patient access through reduced costs.

A key question for health care professionals (HCPs) contemplating prescribing biosimilar drugs is “Should the biosimilar immediately replace the reference product currently in use by the stable patient?” When considering this, HCPs should take into account not only the efficacy and safety of the biosimilar, but also any possible effects of switching patients

from the reference to its biosimilar product. Such effects can be identified by clinical and real-world studies of switching. With each approach, the goal is to demonstrate no loss of efficacy or increase in safety risk when transitioning patients between the two compounds. However, regulatory agencies generally do not require switching studies in order to approve a biosimilar, resulting in registration studies that do not always assess the effects of switching patients between treatments. The United States Food and Drug Administration (US FDA) is an exception to this, requiring a single transition evaluation to demonstrate that a biosimilar can be switched with a reference product [6], and a study with three reference → biosimilar switches to demonstrate interchangeability [7]. When switching data are unavailable to inform clinical decisions, this may negatively impact the HCP’s ability to offer optimal treatment.

Clinical and real-world studies conducted using scientifically sound methodology and that have an appropriate trial design provide the highest levels of evidence that a reference compound can be effectively switched with its biosimilar.

Trial designs of biosimilar switching studies have been discussed previously [8–10], and six elements are considered necessary to fully demonstrate the safety of switching between reference biologic and biosimilar drugs [10–12] (Fig. 1). Studies can incorporate these elements in several different ways (Fig. 1) and can be transition studies (patients receiving treatment A switch to B, but not vice versa), switch studies (patients receiving treatment A switch once to B while those receiving B switch once to A), or interchangeability studies (patients switch treatments multiple times) [8, 13].

Several proposed biosimilars of the reference biologics infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira), and rituximab (MabThera/Rituxan) are in development, and six compounds have been approved by either the European Medicines Agency (EMA) [14] or the FDA [15] (Table 1). The level of available evidence regarding switching varies greatly for these treatments. This review assesses the current body of switching data for these reference biologics and their respective biosimilars and proposed biosimilars.

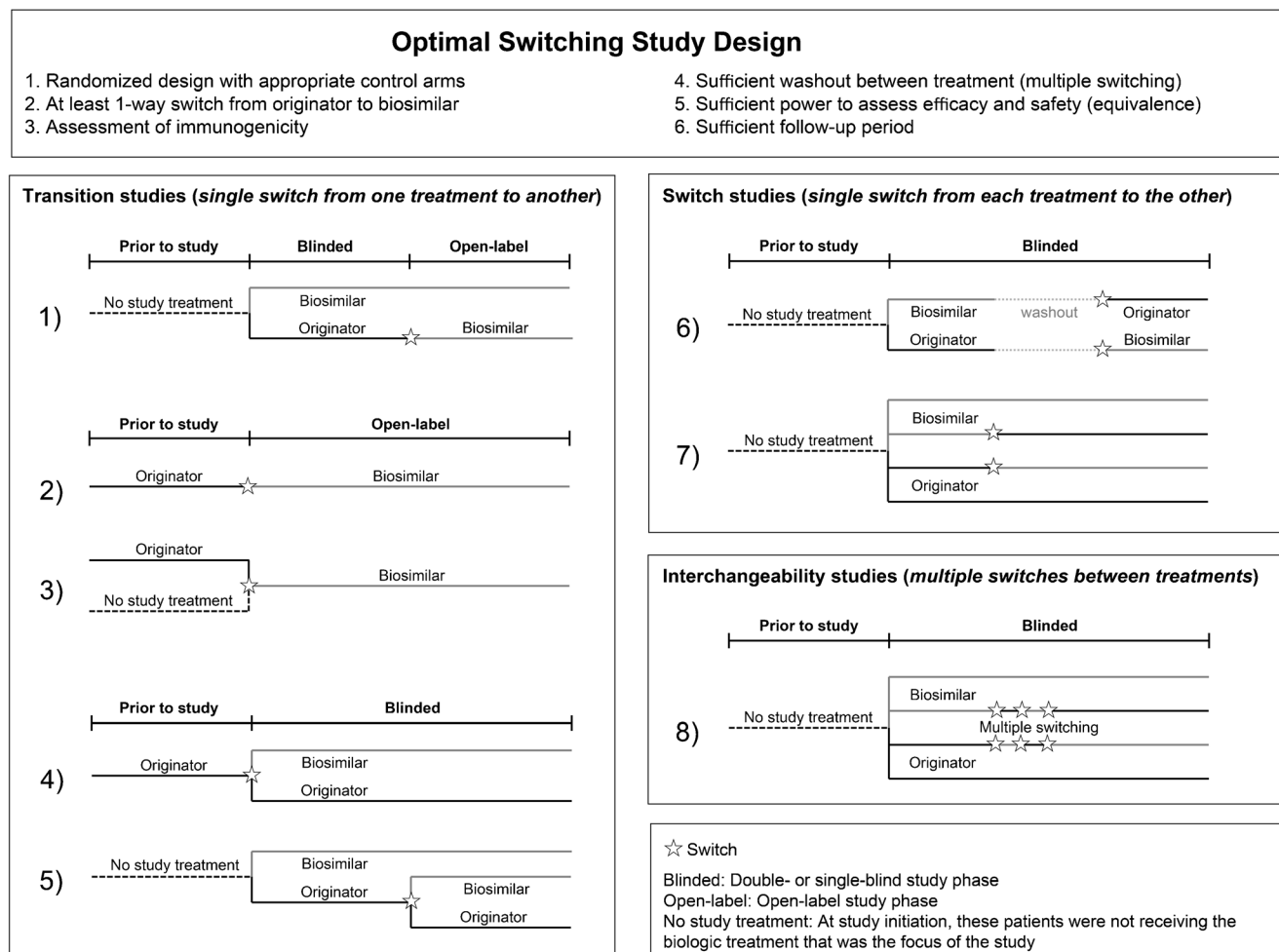


Fig. 1 Elements of the optimal switching study and study designs employed by switching studies of reference biologics and biosimilars

Table 1 Approval status of proposed biosimilars of infliximab, etanercept, adalimumab, and rituximab

Biologic reference	Biologic copy	Regulatory body							
		EMA				FDA			
		Approval status	Date	Proprietary name(s)	Designation	Approval status	Date	Proprietary name(s)	Designation
Infliximab	CT-P13	Approved [14]	September 2013	Inflixtra/Remsima	Biosimilar	Approved [15]	April 2016	Inflixtra	Biosimilar
	SB2	Approved [14]	May 2016	Flixabi	Biosimilar	Accepted for regulatory review [16]	May 2016	-	Proposed
Etanercept	SB4	Approved [14]	January 2016	Benepali	Biosimilar	Not submitted for review	-	-	Proposed
	GP2015	MAA accepted for regulatory review [17]	December 2015	n/a	Proposed	Approved [15]	August 2016	Erelzi	Biosimilar
	CHS-0214	Planned MAA submission [18]	Q4 2016	-	Proposed	Not submitted for review	-	-	Proposed
	HD203	Not submitted for review	-	-	Proposed	Not submitted for review	-	-	Proposed
	LBEC0101	Not submitted for review	-	-	Proposed	Not submitted for review	-	-	Proposed
	TuNEX	Not submitted for review	-	-	Proposed	Not submitted for review	-	-	Proposed
Adalimumab	ABP 501	Positive CHMP opinion [19, 20]	January 2017	Amgevita/Solymbic	Proposed	Approved [15]	September 2016	Amjevita	Biosimilar
	SB5	MAA accepted for regulatory review [21]	July 2016	-	Proposed	Not submitted for review	-	-	Proposed
	M923	Not submitted for review	-	-	Proposed	Not submitted for review	-	-	Proposed
Rituximab	CT-P10	MAA submitted for review [22]	November 2015	-	Proposed	Not submitted for review	-	-	Proposed
	GP2013	MAA accepted for regulatory review [23]	May 2016	-	Proposed	Not submitted for review	-	-	Proposed

Abbreviations: CHMP Committee for Medicinal Products for Human Use, EMA European Medicines Agency, FDA United States Food and Drug Administration, MAA marketing authorization application, Q4 fourth quarter

Methodology

We conducted a search (31 October 2016) of PubMed and Web of Knowledge to identify studies where patients being treated with infliximab, etanercept, adalimumab, or rituximab for conditions in the areas of rheumatology, gastroenterology, and dermatology switched from the reference product to a biosimilar or proposed biosimilar. The International Clinical Trials Registry Platform was searched to identify unpublished clinical trials involving reference biologic → biosimilar switch(es). Selected congresses were hand-searched to identify abstracts not indexed at the time of the literature search. Search details are available in Online Resource Tables 1 and 2. The effect of switching on the three clinical areas of drug efficacy, safety, and immunogenicity was noted for each published study.

Results

Switching Between Reference and Biosimilar/Proposed Biosimilar Infliximab

Many clinical and observational studies involving a switch between reference infliximab and its biosimilars CT-P13 [24, 25•, 26, 27•, 28, 29, 30•, 31•, 32•, 33•, 34•, 35–64, 65•, 66•, 67–72] (EMA/FDA-approved), SB2 [73•, 74•] (EMA-approved), and NK [75] (Japanese Pharmaceuticals and Medical Devices Agency-approved) have been conducted or are ongoing (Table 2). Some studies report switching data but do not identify the biosimilar used [76, 77].

Data have been published from 26 studies of reference infliximab → CT-P13 switching (23 completed, 3 ongoing) in

Table 2 Studies of reference and biosimilar infliximab, etanercept, adalimumab, and rituximab incorporating a switch protocol

Innovator	Biosimilar	Sponsor study name (trial registration)	Study design (study type ^a)	Indication(s)	Number of patients	Switches/ patient	Follow-up post-switch	Status (predicted completion date)	Switching data published?
Infliximab	CT-P13	PLANETRA (NCT01217086)	OL extension to phase III DB RCT (transition, design 1)	RA	302	1	48 weeks	Completed	Yes [24, 25]
Infliximab	CT-P13	PLANETAS (NCT01220518)	OL extension to phase I DB RCT (transition, design 1)	AS	174	1	48 weeks	Completed	Yes [26, 27]
Infliximab	CT-P13	(JapicCTI-142419) Tanaka	OL extension to phase I/II RCT (transition, design 1)	RA	71	1	134 weeks	Completed	Yes [28]
Infliximab	CT-P13		Database analysis (transition, design 2)	RA	3018	1	Variable	Completed	Yes [29]
Infliximab	CT-P13	DANBIO	Registry analysis (transition, design 2)	RA, PsA, AxSpA	792	1	11 months	Completed	Yes [30, 31, 32, 33, 34]
Infliximab	CT-P13		Single-center study (transition, design 2)	RA, AS, PsA, enteropathic arthritis	56	1	Variable	Completed	Yes [35]
Infliximab	CT-P13		Single-center study (transition, design 2)	AS, enteropathic arthritis, PsA, undifferentiated SpA	41	1	26 weeks	Completed	Yes [36–38]
Infliximab	CT-P13		Single-center study (transition, design 2)	RA, SpA, PsA, JRA, chronic reactive arthritis	39	1	Variable	Completed	Yes [39, 40]
Infliximab	CT-P13		Single-center study (transition, design 2)	Inflammatory arthritis	34	1	n/a	Completed	Yes [41]
Infliximab	CT-P13		Single-center study (transition, design 2)	RA, AS, PsA	30	1	n/a	Completed	Yes [42]
Infliximab	CT-P13	BIO-SWITCH (NTR5279)	Observational OL, phase IV (transition, design 4)	RA, SpA, PsA	192	1	52 weeks	Ongoing (April 2017)	Partly [43]
Infliximab	CT-P13		Single-center study (transition, design 2)	CD, UC	143	1	6 months	Completed	Yes [44]
Infliximab	CT-P13		Single-center MSP (transition, design 2)	IBD	134	1	16 weeks	Completed	Yes [45]
Infliximab	CT-P13		Retrospective OL (transition, design 3)	CD, UC	110	1	Variable	Completed	Yes [46, 47]
Infliximab	CT-P13		Observational cohort (transition, design 2)	CD, IBD, UC	83	1	16 weeks	Completed	Yes [48, 49]
Infliximab	CT-P13		Single-center study (transition, design 3)	CD	75	1	26 weeks	Completed	Yes [50]
Infliximab	CT-P13		Prospective (transition, design 2)	CD, UC	74	1	24 weeks	Completed	Yes [51, 52]
Infliximab	CT-P13		Single-center study (transition, design 3)	UC	40	1	26 weeks	Completed	Yes [53]
Infliximab	CT-P13		Observational OL (transition, design 2)	Pediatric CD and UC	39	1	32 weeks	Completed	Yes [54–57]
Infliximab	CT-P13		Single-center study (transition, design 3)	CD, UC	25	1	48	Completed	Yes [58]

Table 2 (continued)

Innovator	Biosimilar	Sponsor study name (trial registration)	Study design (study type ^a)	Indication(s)	Number of patients	Switches/ patient	Follow-up post-switch	Status (predicted completion date)	Switching data published?
Infliximab	CT-P13		Retrospective OL (transition, design 3)	CD, UC	17	1	n/a	Completed	Yes [59, 60]
Infliximab	CT-P13		Observational (transition, design 3)	CD, UC	397	n/a	Variable	Ongoing (unknown)	Partly [61, 62]
Infliximab	CT-P13		OL, phase 4 (transition, design 3)	CD, FCD, UC	173	1	30 weeks	Ongoing (unknown)	Partly [63]
Infliximab	CT-P13		Single-center study (transition, design 3)	PsO	35	1	Variable	Completed	Yes [64]
Infliximab	CT-P13	NOR-SWITCH (NCT02148640)	DB RCT, phase 4 (transition, design 4)	RA, SpA, PsA, UC, CD, PsO	481	1	52 weeks	Completed	Yes [65, 66]
Infliximab	CT-P13		Single-center study (transition, design 2)	PsA, AS, RA, CD, Behçet's disease	23	1	n/a	Completed	Yes [67]
Infliximab	CT-P13	(JapicCTI-142,703)	OL extension to phase IV RCT (transition, design 1)	RA	n/a	1	n/a	Completed	No [68]
Infliximab	CT-P13	SIMILAR (2015-001954-14)	Phase IV DB RCT, OL extension planned (transition, design 4)	UC, CD	182	1	30 weeks	Ongoing (August 2016)	No [69]
Infliximab	CT-P13	(NCT02096861)	DB RCT, phase III (substitution, design 7)	CD	220	n/a	n/a	Ongoing (February 2017)	No [70]
Infliximab	CT-P13	CONNECT-IBD (NCT02539368)	Observational, phase IV (transition, design 2)	CD, UC	n/a	n/a	n/a	Ongoing (June 2019)	No [71]
Infliximab	CT-P13	SECURE (2014-004904-31)	OL (no comparator), phase IV (transition, design 2)	RA, UC, CD	n/a	1	16 weeks	Ongoing (March 2016)	No [72]
Infliximab	SB2	(NCT01936181)	DB RCT, phase III (transition, design 5)	RA	396	1	24 weeks	Completed	Yes [73, 74]
Infliximab	Infliximab NK		Single-center (transition, design 3)	UC, CD	20	1	22 weeks	Completed	Yes [75]
Infliximab	Unspecified		Retrospective OL (transition, design 2)	IBD	72	1	26 weeks	Completed	Yes [76]
Infliximab	Unspecified	(UMIN 000021492)	OL single-center study (transition, design 2)	RA	40	1	n/a	Ongoing (unknown)	No [77]
Etanercept	SB4	(NCT01895309)	OL extension of phase III RCT (transition, design 1)	RA	245	1	48 weeks	Completed	Yes [78, 79]
Etanercept	SB4	(NCT01865552)	SB RCT, phase III (substitution, design 6)	-	138	1	28 days	Completed	Yes [80, 81]
Etanercept	SB4	BIO-SPAN (NTR5901)	OL single-center study (transition, design 2)	Rheumatic disease	500	1	52 weeks	Ongoing (December 2017)	No [82]
Etanercept	GP2015	EGALITY (NCT01891864)	DB RCT, phase III (interchangeability, design 8)	PsO	531	3	40 weeks	Completed	Yes [83]
Etanercept	GP2015	2012-002011-26)	DB RCT, phase I (substitution, design 6)	-	54	1	28 days	Completed	Yes [84]

Table 2 (continued)

Innovator	Biosimilar	Sponsor study name (trial registration)	Study design (study type ^a)	Indication(s)	Number of patients	Switches/ patient	Follow-up post-switch	Status (predicted completion date)	Switching data published?
Etanercept	GP2015	EQUIRA (2012-002009-23) (NCT01431404)	DB RCT, phase III (transition, design 1)	RA	366	1	24 weeks	Ongoing (September 2017)	No [85]
Etanercept	HD203	(NCT01431404)	DB SD crossover, phase I (substitution, design 6)	–	42	1	21 days	Completed	No [86]
Etanercept	CHS-0214	Rapsody (NCT02115750)	DB RCT, phase III (transition, design 1)	RA	647	1	n/a	Completed	No [87]
Etanercept	LBEC0101	(NCT01725620)	DB SD crossover, phase I (substitution, design 6)	–	48	1	27 days	Completed	No [88]
Etanercept	LBEC0101	(NCT01145950)	DB SD crossover, phase I (substitution, design 6)	–	36	1	22 days	Completed	No [89]
Etanercept	LBEC0101	(NCT02715908)	OL extension of phase III RCT (transition, design 1)	RA	165	1	48 weeks	Ongoing (March 2018)	No [90]
Etanercept	TuNEX	(ICTRP KCT0000118)	OL SD crossover, phase I (substitution, design 6)	–	23	1	21 days	Completed	No [91, 92]
Adalimumab	ABP 501	(NCT02114931)	OL extension of phase III RCT (transition, design 1)	RA	467	1	48 weeks	Completed	Yes [93•]
Adalimumab	ABP 501	(NCT01970488)	DB RCT, phase III (transition, design 5)	PsO	350	1	36 weeks	Completed	Yes [94, 95]
Adalimumab	SB5	(NCT02167139)	DB RCT, phase III (transition, design 5)	RA	273	1	28 weeks	Completed	Yes [96•, 97•]
Adalimumab	M923	(2015-001751-76)	DB RCT, phase III (transition, design 5)	PsO	516	Multiple	13 weeks	Ongoing (March 2017)	No [98]
Rituximab	CT-P10	(NCT01873443)	OL extension to phase I RCT (transition, design 1)	RA	87	1	56 weeks	Completed	Yes [99•]
Rituximab	GP2013	ASSIST-RT (NCT02514772)	DB RCT, phase III (transition, design 4)	RA	107	1	12 weeks	Ongoing (December 2016)	No [100]

^a As illustrated in Fig. 1

Abbreviations: AS ankylosing spondylitis, AxSpA axial spondyloarthritis, CD Crohn's disease, DB double-blind, FCD fistulizing active Crohn's disease, IBD inflammatory bowel disease, JRA juvenile rheumatoid arthritis, MSP managed switching program, n/a information not available, OL open-label, PsA psoriatic arthritis, PsO psoriasis, RA rheumatoid arthritis, RCT randomized controlled trial, SpA spondyloarthritis, UC ulcerative colitis

various indications: rheumatic disease [24, 25•, 26, 27•, 28, 29, 30•, 31•, 32•, 33•, 34•, 35–43] ($n = 11$); inflammatory bowel disease [44–63] ($n = 12$); psoriasis (PsO) [64] ($n = 1$); and multiple disease areas [65•, 66•, 67] ($n = 2$). All these studies are transition studies (single switch from reference → biosimilar), although the precise designs used vary (Table 2). Switching data are available in Online Resource Table 3).

Three of the 10 completed reference infliximab → CT-P13 switching studies in patients with rheumatic disease are open-label extensions (OLEs) of double-blind (DB) studies (study design 1, Fig. 1). In the PLANETRA [24, 25•], PLANETAS [26, 27•], and Tanaka et al. [28] studies, patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS) who completed a DB clinical trial of CT-P13 [101–103] enrolled in an OLE; patients who received reference infliximab in the DB stage switched to CT-P13. In all three studies, clinical measures of efficacy were similar in the switched and non-switched groups at study end. Efficacy was also similar pre- and post-switch in the switched groups. In the PLANETRA and Tanaka et al. studies, clinical measures of safety were comparable between non-switched and switched groups [24, 25•, 28]. In the PLANETAS study, the proportion of patients with ≥ 1 treatment-emergent adverse event (TEAE) was higher in the switched group (71.4%) than the non-switched group (48.9%) [26, 27•]. However, rates of TEAEs in both groups during both phases of the PLANETAS study were within the range reported historically in studies of reference infliximab in patients with AS [104–110] and were mild or moderate in severity [26, 27•]. In all studies, immunogenicity was comparable between the non-switched and switched groups at study end, and anti-drug antibody (ADAb) positivity did not increase in the OLE versus the DB stage [24, 25•, 26, 27•, 28].

The other seven completed studies of infliximab → CT-P13 switching in patients with rheumatic disease are either database/registry analyses [29, 30•, 31•, 32•, 33•, 34•] or small (30–56 patients) single-center studies [35–42] with no comparator arms (Fig. 1, study design 2). As with the clinical trials described above, efficacy and safety outcomes were usually similar pre- and post-switch, although one study reported a significant reduction in duration of morning stiffness following switch to CT-P13 [36]. The DANBIO registry study in patients with various rheumatic diseases found that 117/768 (15%) of patients discontinued treatment between switching and end of follow-up (median 336 days) for reasons including AEs (34 patients) and loss of efficacy (51) [33•]. Only two studies reported immunogenicity outcomes, with no change in ADAb levels reported before/after switching [31•, 32•, 36].

The final study in patients with rheumatic disease, which is still ongoing, is the BIO-SWITCH study. Interim data showed that patients with spondyloarthritis (SpA), but not RA or psoriatic arthritis (PsA), experienced significantly enhanced mean disease activity 6 months post-switch. The number of patients

with ADAbs decreased from study baseline to end, but the significance of this was not discussed [43].

The 12 published studies of reference infliximab → CT-P13 switching in patients with inflammatory bowel disease were predominantly open-label (OL) observational studies utilizing study design 2 or 3 (Fig. 1) and were of various sizes (17–143 patients) and duration (Table 2) [44–63]. All studies except for one [45] reported efficacy outcomes, with no significant differences generally found between reference infliximab and CT-P13. In the PROSIT-BIO study, a significantly higher proportion of patients who switched from reference infliximab to CT-P13 (12%) experienced a loss of treatment response over 6 months, compared with patients receiving CT-P13 who were anti-TNF- α -naïve (1%) or who had previous exposure to a biologic (5%) [61, 62]. All 12 studies reported safety outcomes, and none reported any differences in safety profile between reference infliximab and CT-P13. Four studies reported immunogenicity data [44, 48, 49, 51, 52, 57]; two compared ADAb positivity pre- and post-switch, reporting no increase in immunogenicity from time of switch to study end [51, 52, 57].

One small single-center transition study was conducted in patients with PsO [64] (design 3, Fig. 1). Efficacy and safety outcomes were similar pre- and post-switch. Immunogenicity was not assessed.

Two studies were conducted across multiple indications [65•, 66•, 67]. The first was the NOR-SWITCH study; a large phase IV DB randomized controlled trial (RCT) (design 4, Fig. 1) in patients with various inflammatory conditions [Crohn's disease (CD; $n = 155$, 32.2%), ulcerative colitis (UC; $n = 93$, 19.3%), SpA ($n = 91$, 18.9%), RA ($n = 77$, 16.0%), PsA ($n = 30$, 6.2%), and PsO ($n = 35$, 7.3%)]. Switching from reference infliximab to CT-P13 was not inferior to continued treatment with the reference product. Disease worsening (study primary endpoint), other measures of disease, and incidence of ADAbs were similar for patients receiving reference infliximab versus CT-P13 across all diseases [65•, 66•]. The second study was a small single-center transition study (design 2, Fig. 1) of patients in disease remission who switched treatments. Relapse occurred in seven (30%) patients after a mean of 1.7 months of CT-P13 treatment; these patients switched back to reference infliximab and improvements were seen in five (71%) of these patients. Immunogenicity was not assessed [67].

There are currently five unpublished studies (one completed, four ongoing) evaluating switching between reference infliximab and CT-P13. The completed study, in patients with RA (JapicCTI-142,703 [68]), is an OLE of a DB RCT [103] with patients receiving reference infliximab in the DB phase and CT-P13 in the OLE constituting the switch group (design 1, Fig. 1). The four ongoing unpublished studies of reference infliximab and CT-P13 are of various design [three transition studies [69, 71, 72] of designs 2 and 4, and one switch study

[70] of design 7 (Fig. 1)]. Two studies are DB RCTs [69, 70] and two are OL observational studies [71, 72]. SIMILAR [69] will randomize patients in a blinded manner to either continue their current treatment or switch to CT-P13. Study NCT02096861 [70] will have four treatment arms: (1) reference infliximab throughout; (2) switch from reference infliximab → CT-P13; (3) CT-P13 throughout; (4) switch from CT-P13 → reference infliximab. CONNECT-IBD [71] will follow patients who have been prescribed reference infliximab or CT-P13 and document any switches and reasons for switching. SECURE [72] will switch all patients to CT-P13.

Overall, CT-P13 switching data suggest that it is well tolerated and effective in different patient populations and that reference → CT-P13 switching has no effect on treatment efficacy or safety. CT-P13 immunogenicity data have been reported in 12/26 studies and show no difference in ADAB incidence between reference infliximab and this biosimilar product (Online Resource Table 3). The question still remains as to why some patients who are stable on reference infliximab, sometimes for several years, discontinue treatment with the biosimilar after switching.

The biosimilars SB2 [73•, 74•] and infliximab NK [75] each have a single switching study. The SB2 study, in patients with RA, is a transition study [73•, 74•] (design 5, Fig. 1). Patients receiving reference infliximab for the first 54 weeks were re-randomized to receive either reference infliximab or SB2 for an additional 24 weeks. Patients receiving SB2 in the main study did not switch treatments. The efficacy, safety, and immunogenicity profiles were comparable between the three treatment groups. The infliximab NK study, in patients with CD or UC, is a transition study [75] (design 3, Fig. 1). In this single-center study, patients previously receiving reference infliximab switched to infliximab NK, and patients who were anti-TNF- α -naïve started treatment with infliximab NK. Remission was maintained in switched patients and achieved by 80–100% of NK-induced patients (depending on indication). No differences in safety were noted between groups. Immunogenicity outcomes were not reported.

As each product must be considered separately, the current body of data on these infliximab biosimilars (SB2 and NK, each with only a single switching study) requires further data and follow-up by pharmacovigilance, registry data and/or additional studies to demonstrate the safety of switching between these infliximab biosimilar products.

Switching Between Reference and Biosimilar/Proposed Biosimilar Etanercept

The switching studies conducted on reference etanercept and its biosimilars, and proposed biosimilars cover six different products (Table 2). These are the EMA-approved biosimilar SB4, the FDA-approved biosimilar GP2015, and the Korean

Ministry of Food and Drug Safety-approved biosimilar HD203 (not EMA/FDA-approved). Three other compounds, CHS-0214, LBEC0101, and TuNEX, are still under development (Table 1). Nine studies of these biosimilars and proposed biosimilars are completed (four with published switching data) and three are ongoing. Details regarding efficacy, safety, and immunogenicity of switching between reference etanercept and its various biosimilars and proposed biosimilars are available in Online Resource Table 3.

SB4 is the only EMA-approved biosimilar of etanercept. Three SB4 studies utilize a switching protocol and two have published switching data. The first is an OLE of a phase III DB study of etanercept and SB4 (transition study, design 1, Fig. 1) [78•, 79•]. The second is a phase I, randomized, single-blind crossover study (with washout) of the pharmacokinetics (PK) of etanercept and SB4 (switch study, design 6, Fig. 1) [80, 81]. In the phase III trial, patients with RA were randomized to receive etanercept or SB4 for an initial 52 weeks [111], after which patients receiving etanercept switched to SB4 for a further 48 weeks [78•, 79•]. Clinical measures of efficacy were similar for switched and non-switched patients at study end and were similar pre- and post-switch. Safety was similar for switched and non-switched patients at study end; the higher level of hepatobiliary disorders reported with SB4 compared with etanercept (17 vs. 0 adverse events (AEs) [112], all reported pre-switch [111]) was heterogeneous and thought to be due to chance rather than to true SB4 causality [113]. Switching from etanercept to SB4 did not result in any increase in immunogenicity [78•, 79•]. In the phase I trial, the PK of etanercept and SB4 was assessed in a three-part study. Part A involved a transition between European Union (EU)-sourced etanercept and SB4. Part B involved a transition between US-sourced etanercept and SB4. Part C involved a transition between EU- and US-sourced etanercept. In all parts, immunogenicity was assessed before and 28 days after the first dose, but not after the transition. PK parameters were similar for etanercept and SB4 in all parts, but as the study did not provide the data from pre- and post-switch evaluations separately, the effect of the switch on PK parameters was not assessed. There were no discontinuations post-switch [80, 81]. The final switching study of Enbrel and SB4 (BIO-SPAN [82]) is a switching study of etanercept and SB4 in patients with rheumatic disease. This ongoing study is an OL transition study (study design 2, Fig. 1) with all patients switching to SB4.

GP2015 is the only FDA-approved biosimilar of etanercept. Three GP2015 studies utilize a switching protocol and two have published switching data. The first (EGALITY [83•]) is a phase III DB RCT in patients with PsO, incorporating two non-switching arms and two switching arms involving multiple switches (interchangeability study, design 8, Fig. 1). Patients were randomized to treatment with either etanercept or GP2015 for 12 weeks and then re-randomized

to either remain on their current treatment or to undergo repeated switching between treatments (three switches at 6-week intervals to week 30, and then maintain treatment to week 52). Repeated switching had no impact on efficacy, safety, or immunogenicity [83•]. The second GP2015 study is a phase I DB RCT PK study (switch study, design 6, Fig. 1) [84], with the PK of etanercept and GP2015 assessed with a single switch each way. PK parameters were similar for etanercept and GP2015 in all parts, but as the study did not provide the data from pre- and post-switch PK, safety, or immunogenicity evaluations separately, the effect of switching on these outcomes was not assessed [84].

The final switching study of etanercept and GP2015 (EQUIRA [85]) is an ongoing, phase III DB RCT with OLE (transition study, design 1, Fig. 1) in patients with RA, with patients randomized to treatment with etanercept in the DB phase switching to GP2015 in the OLE.

There is no evidence yet to support switching between reference etanercept and any of the proposed biosimilars HD203, CHS-0214, LBEC0101, and TuNEX, but six studies are either completed or ongoing. Four of these studies of etanercept proposed biosimilars are phase I single-dose crossover studies of HD203 [86], LBEC0101 [88, 89], and TuNEX [91, 92]. One study is a phase III DB RCT of CHS-0214 [87], and one is an OLE of a phase III DB RCT of LBEC0101 [90] (Table 2). No switching data are yet available from these studies.

Overall, data showing the safety of switching of reference etanercept to a biosimilar are only available for SB4 and GP2015, and for each data are only available from two studies (one phase I study and one phase III). The safety of transition and switching between reference etanercept and its proposed biosimilars requires follow-up by pharmacovigilance, registry data, and/or additional studies in order to provide sufficient long-term real-world data.

Switching Between Reference and Biosimilar/Proposed Biosimilar Versions of Adalimumab and Rituximab

ABP 501 is the only EMA/FDA-approved biosimilar of adalimumab, and there are no EMA- or FDA-approved biosimilars of rituximab. Compared with infliximab and etanercept, there are very few adalimumab or rituximab reference → biosimilar/proposed biosimilar switching studies (Table 2). Details of the published studies are available in Online Resource Table 3.

There are two switching studies of adalimumab and its biosimilar ABP 501 (two transition studies, designs 1 [93•] and 5 [94, 95]; Fig. 1). One is a phase III DB RCT in patients with PsO [94, 95], while the other is an OLE to a phase III RCT in patients with RA [93•]. In the RA study, patients were randomized to DB treatment with either reference adalimumab or ABP 501 for 24 weeks. Patients randomized

to treatment with reference adalimumab then switched to OL ABP 501, and patients receiving ABP 501 continued treatment. Post-switch, efficacy was reported as being maintained with no new safety findings. Long-term safety and efficacy results were reported to be similar between patients who switched from reference adalimumab and those who continued treatment with ABP 501; however, the necessary data to compare switched and non-switched patients are not available [93•]. In the PsO study, patients were first randomized to treatment with reference adalimumab or ABP 501 for 16 weeks; patients receiving reference adalimumab were then re-randomized to either continue treatment with reference adalimumab or switch to ABP 501. No efficacy or safety data were presented, but immunogenicity was not affected by switching treatments [94, 95].

The studies of the proposed adalimumab biosimilars SB5 and M923 are both phase III DB RCTs. The SB5 study is a transition study (design 5, Fig. 1) conducted in patients with RA [96•, 97•]. Patients were first randomized to treatment with reference adalimumab or SB5 for 24 weeks; patients receiving reference adalimumab were then re-randomized to either continue treatment with reference adalimumab or switch to SB5. Switching had no impact on efficacy, safety, or immunogenicity. The M923 study is an ongoing transition study (design 5, Fig. 1) in patients with PsO [98]. Patients will be randomized to treatment with reference adalimumab or M923; some patients receiving reference adalimumab will later switch to M923.

There are two switching studies of reference rituximab and its proposed biosimilars CT-P10 [99•] and GP2013 [100]. The CT-P10 study is a transition study (design 1, Fig. 1), an OLE [99•] of a phase I DB RCT [114] in patients with RA. Clinical measures of efficacy and safety were similar in the switched and non-switched groups. Efficacy pre- and post-switch could not be compared as different efficacy measures were reported for the DB [114] and OLE [99•] phases of the study. Immunogenicity was only assessed pre-switch. ASSIST-RT [100] is an ongoing switching study of GP2013 in which patients with RA already receiving reference rituximab will be randomized to either continue treatment or switch to GP2013.

Data regarding switching of reference adalimumab or rituximab and their biosimilars/proposed biosimilars are limited and the safety of switching has not yet been sufficiently demonstrated.

Considerations Around Switching from Biologics to Biosimilars

Switching between reference biologics and biosimilar versions is a therapeutic transition based on prescriber decision. Medical switching should be performed by the prescriber for clinical reasons, such as optimizing efficacy or minimizing

AEs. The potential for financial savings with biosimilars [115] makes it likely that switching between reference biologics and biosimilars will take place for non-medical reasons as no changes in clinical outcomes are expected after switching.

Any decision to switch biologic treatments should remain a clinical decision made by the treating physician on a case-by-case basis, with full patient awareness, and supported by scientific evidence. Many factors must be considered. Switching data is not transferable between different biologics or between different biosimilars of the same biologic. Differences in the incidence or type of AEs upon switching must also be considered; even large RCTs for biosimilars are not powered to show the significance of the difference when rare, unexpected AEs occur [12]. In addition, clinical trials have stringent inclusion and exclusion criteria that may not appropriately reflect the real-world patient seen by HCPs. For instance, trials conducted in patients who are naïve to biologic treatment are not reflective of patients who are stable on a reference biologic. Clinical trials also need to balance the need for using a sensitive population (one most able to demonstrate the looked-for phenomenon) versus an appropriate population (one with a condition for which the treatment is indicated) [116]. Switching studies in stable patients must be interpreted with caution as the definition of “stable” varies between studies and can refer to both the clinical status of the patient and the dose of the existing medication being taken. Furthermore, pediatric and elderly populations and those with comorbidities are often under-represented in clinical trials [117–119]. The ability of the patient to adapt to changes when switching to a biosimilar also needs to be considered, especially if patients require instruction regarding a new injection device. Patient status is therefore a key consideration when weighing the pros and cons of switching to a biosimilar. Even when comprehensive data from clinical studies are available, it may not be appropriate to switch all patients.

Careful pharmacovigilance and use of patient registries to document rare AEs are critical in order to gather clinical evidence of the benefits and risks of switching in all patients. There is a need for national databases capturing details of biologic switching so that a full picture of the safety of even relatively infrequent switching of biosimilar products can be obtained. Effective pharmacovigilance will be as important as it currently is for reference biologics.

Recommendations Regarding Switching to Biosimilars

In order to safeguard patient safety, we propose the following recommendations regarding switching between reference and biosimilar treatments:

(1) The decision to switch should be based on scientifically sound (including real-world) data.

(2) Switching between reference biologic and biosimilar products, or between different biosimilar products, should

remain a clinical decision to be made by the treating physician on an individual patient basis with patient awareness.

(3) Switching data from one biologic molecule should not be used to inform switching decisions between other biologic/biosimilar treatments.

(4) Automatic substitution at the pharmacy level should not take place as this decision would not be made by the treating physician.

(5) Patients should be closely followed post-switching to monitor for AEs; data should be made available for national registries that report into large pharmacovigilance databases.

(6) The decision to switch patients from a reference product to its biosimilar should be made on a case-by-case basis depending on the underlying disease, patient characteristics and comorbidities, type of reference drug, and patient willingness to switch.

Conclusions

The introduction of biosimilar versions of established biologic drugs used in a range of inflammatory diseases provides an opportunity to greatly increase patient access to treatment. The safety of switching to these biosimilars has not yet been fully demonstrated in terms of their long-term efficacy, safety, and immunogenicity. Thus, data from pharmacovigilance programs are needed in order to adequately inform clinical decision-making in relation to switching between these compounds. However, as the information gap is filled (particularly with data derived from appropriately designed switching clinical trials and real-world experience), we believe treatment practice will adapt.

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