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Biosimilars in rheumatology: A review of the evidence and their place in the treatment algorithm

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Abstract

Determining biosimilarity involves a comprehensive exercise with a focus on determining the comparability of the molecular characteristics and preclinical profile of the biosimilar and reference product, such that there is less need for extensive clinical testing to assure comparability of clinical outcomes. Three anti-TNF biosimilar agents are approved for patients with rheumatic diseases in the European Union. The infliximab (Remicade®) biosimilars CT-P13 (Remsima® and Inflectra®) and SB2 (Flixabi®) and the etanercept (Enbrel®) biosimilar SB4 (Benepali®) have shown close comparability to their reference medicinal products, having undergone extensive evaluations. Guidelines on the treatment of rheumatic diseases have acknowledged that biosimilars and biologic DMARDs (bDMARDs) are interchangeable in clinical practice, except when patients experience lack of efficacy or tolerability with the reference agent. Given that cost is a barrier to effective bDMARD use, the introduction of less costly biosimilars is likely to widen access and dissipate treatment inequalities. Physicians faced with prescribing decisions should be reassured by the robust and exhaustive process that is involved in assuring comparability of biosimilars with their reference agents. *De novo* usage of a biosimilar and switching to a biosimilar following lack of efficacy or tolerability with a different reference biologic agent are likely to be strategies most easily adopted, although switching during successful treatment should also be considered given the potential cost implications. The introduction of biosimilar bDMARDs has the potential to improve patient access to effective biologic therapy, to better accommodate restraints within healthcare budgets and to improve overall patient outcomes.

Key words: biosimilar, CT-P13, rheumatic disease, SB2, SB4

REVIEW

Rheumatology key messages

- CT-P13 and SB2 (infliximab biosimilars) and SB4 (etanercept biosimilar) are approved for the treatment of several rheumatic diseases.
- Biosimilars and their reference agents have been shown to be interchangeable.
- Introduction of biosimilars may widen access to biologic therapy and improve overall patient outcomes.

Introduction

Biologic agents are an important therapeutic option in the treatment of patients with rheumatic diseases, including RA [1], AS [2] and PsA [3]. Guidelines and recommendations for the use of biologic agents, and anti-TNF agents in particular, do not prioritize the use of any one of these agents [2–8]. Therefore, the choice of the biologic agent for a particular patient may hinge on other clinical considerations, such as dosing frequency, route and mode of administration, the presence of comorbidities and the safety/adverse-event profile of the candidate drug [1].

Despite the fact that biologic agents are highly effective in the treatment of rheumatic diseases, and are often considered to be cost-effective for patients who have not responded adequately to conventional treatment, patients are unlikely to be treated with these agents first-line, and may even encounter barriers to their use as second-line therapy [9]. This, in part, reflects the high costs of these agents and administrative restrictions [9]. Furthermore, among those patients who receive a biologic

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treatment, a significant proportion of patients either do not respond to initial treatment or lose responsiveness [10], and more than 1 in 10 patients typically withdraws due to side effects [11]. Access to biologic agents *per se*, and to a wider range of alternative biologic agents, is therefore a key consideration in improving the treatment, and therefore outcomes, for patients with rheumatic diseases. The development of biosimilar agents that are highly comparable to the reference medicinal product provides a new route to achieving this goal. This article provides an overview of the biosimilar agents that are currently in development, or available in the clinic, for the treatment of patients with rheumatic diseases, summarizes results from some key clinical trials and discusses the potential place of biosimilars in current rheumatic disease treatment algorithms.

Introducing biosimilars in the treatment of rheumatic disease

Determining biosimilarity involves a comprehensive exercise to define and compare the characteristics of the biosimilar candidate with that of the reference medicinal product [12]. Compared with novel biologic development, biosimilar development involves a much greater focus on determining comparability of the molecular characteristics and preclinical profile, with head-to-head phases I and III clinical studies conducted thereafter to demonstrate pharmacokinetic equivalence, and to assure comparability in terms of efficacy, safety, immunogenicity and tolerability [12]. Post-marketing monitoring is implemented, for example through pharmacoepidemiological studies, to ensure consistent efficacy and continual monitoring of long-term safety. This robust and comprehensive process is designed to ensure confidence in the clinical profile in terms of comparability [13]. A detailed overview of the concept of biosimilarity and the regulatory requirements that are needed to establish biosimilarity, as defined by the European Medicines Agency (EMA), is provided in the first article of this supplement by Declerck and Rezk. To date, biosimilar innovation in rheumatology has focused on the development of biosimilar versions of infliximab and etanercept.

Infliximab biosimilars

Infliximab (Remicade®) is an anti-TNF agent that is approved for use in adult patients with severe active and/or progressive RA, severe active ankylosing spondylitis, active and progressive PsA, moderate to severe plaque psoriasis, moderately to severely active Crohn's disease and fistulizing active Crohn's disease, and in young people aged 6–17 years with severe active Crohn's disease or ulcerative colitis [14]. To date, two infliximab (Remicade®) biosimilars, CT-P13 (Remsima® and Inflectra®) and SB2 (Flixabi®), have been approved for patients with rheumatic diseases in the European Union (EU).

CT-P13

CT-P13 (Remsima® and Inflectra®) is a biosimilar medicinal product containing infliximab that was approved in the EU in 2013 for use in the treatment of adult patients with RA, PsA or psoriasis, ulcerative colitis, Crohn's disease and in young people with ulcerative colitis or Crohn's disease [15–17]. All major physicochemical characteristics and biologic activities (including affinity for soluble and transmembrane TNF) for CT-P13 have been shown to be highly comparable to those of reference infliximab [18]. However, in the regulatory assessment, a small difference was noted in the amount of afucosylated glycans of CT-P13, translating into a lower binding affinity towards specific Fc receptors and a lower *ex vivo* antibody-dependent cellular cytotoxicity (ADCC) in the most sensitive ADCC assay [15]. This difference was not considered to be clinically meaningful as it did not affect the activity of CT-P13 in experimental models that were considered to be more relevant to the pathophysiological conditions in patients [15].

Evidence of pharmacokinetic equivalence between CT-P13 and reference infliximab was provided by a Phase I, randomized, double-blind, parallel-group study (PLANETAS) of 250 patients with AS [19]. Following administration of either agent, at a dose of 5 mg/kg, primary endpoints [area under the concentration–time curve (AUC) at steady state and observed maximum steady-state serum concentration ($C_{max,ss}$) between weeks 22 and 30] were equivalent for CT-P13 (32 765.8 μgh/ml and 147.0 μg/ml) and infliximab (31 359.3 μgh/ml and 144.8 μg/ml). In addition, the 90% CIs of the geometric mean ratios of both AUC at steady state and $C_{max,ss}$ were contained within the predefined equivalence margin (e.g. 80–125%) [19]. The pharmacokinetic profile of multiple doses of CT-P13 was also shown to be comparable to that of reference infliximab, administered by a 2-h intravenous infusion, in a further on-going, phase I, randomized, double-blind study, which included 19 patients with active RA who were also receiving concomitant MTX (between 12.5 and 25 mg/week, oral dose) [15].

The efficacy of CT-P13 for the treatment of RA was assessed in two randomized, double-blind, multicenter studies: the phase III PLANETRA study [20] and a supportive Japanese phase I/II study [21] (Table 1). In the PLANETRA study, patients (n = 606) with active disease, who were previously unresponsive to MTX, were treated with either CT-P13 or reference infliximab at a dose of 3 mg/kg with MTX and folic acid supplementation (see Fig. 1A). This trial met its primary end point for equivalence of efficacy as the 95% CI for the difference in the ACR20 response rate at week 30 was contained within the predefined equivalence margin (e.g. ±15%) in the intention-to-treat population (CT-P13, 60.9%; reference infliximab, 58.6%; 95% CI: −6, 10). Other secondary endpoints, including ACR50 and ACR70 response rates, demonstrated similar results with CT-P13 and reference infliximab at week 30 [20] (Table 1). Likewise, CT-P13 and reference infliximab also did not significantly differ in terms of disease activity measures at week 30, including improvements in Clinical Disease

Table 1 Published clinical studies comparing biosimilar and originator agents

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
CT-P13 *vs* reference infliximab (INX): multinational efficacy and safety studies in patients with RA						
Yoo *et al.* [20] PLANETRA study to week 30	Phase III, randomized, double-blind multicenter multinational, parallel-group study RA patients[a] CT-P13 (n = 302) INX (n = 304)	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8 wks + MTX 12.5-25 mg/wk + folic acid ⩾5 mg/wk	ACR20 response rate CT-P13: 60.9% INX: 58.6% (95% CI: −6, 10) ACR50 response rate CT-P13: 35.1% INX: 34.2% ACR70 response rate CT-P13: 16.6% INX: 15.5% Mean improvement in CDAI CT-P13: −25.2 INX: −23.6 Mean improvement in SDAI CT-P13: −25.8 INX: −24.4 DAS28/CRP response rate CT-P13: 40.9% INX: 39.0% Good/moderate EULAR response (CRP) CT-P13: 85.8% INX: 87.1% (95% CI: 0.92, 1.06)	ADAs at week 14 CT-P13: 25.4% INX: 25.8% ADAs at week 30 CT-P13: 48.4% INX: 48.2%	Overall TEAEs CT-P13: 60.1% INX: 60.8% TEAEs related to treatment CT-P13: 35.2% INX: 35.9% Most frequently reported TEAEs related to treatment CT-P13: latent TB, increased ALT, increased AST, flare of RA activity INX: latent TB, increased ALT, increased AST, UTI Serious TEAEs CT-P13: 10.0% INX: 7% No deaths	CT-P13 demonstrated equivalent efficacy to INX at week 30, with a comparable PK profile and immunogenicity CT-P13 was well tolerated, with a safety profile comparable to that of INX
Yoo *et al.* [22] PLANETRA study extension to week 54	Phase III, randomized, double-blind multicenter, multinational, parallel-group study RA patients[a] CT-P13 (n = 302) INX (n = 304)	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 12.5 − 25 mg/wk + folic acid ⩾5 mg/wk	ACR20 response rate CT-P13: 74.7% INX: 71.3% (95% CI: −0.05, 0.12) ACR50 response rate CT-P13: 43.6% INX: 43.1% ACR70 response rate CT-P13: 21.3% INX: 19.9% Mean improvement in CDAI CT-P13: −25.7 INX: −24.0 Mean improvement in SDAI CT-P13: −26.3 INX: −24.6 Mean improvement in DAS28/CRP CT-P13: −2.3 INX: −2.2 Good/moderate EULAR response (CRP) CT-P13: 87.4% INX: 82.5%	ADAs at week 54 CT-P13: 41.1% INX: 36.0%	Overall TEAEs CT-P13: 70.5% INX: 70.3% TEAEs related to treatment CT-P13: 43.7% INX: 45.0% Most frequently reported TEAEs related to treatment CT-P13: infusion-related reaction, upper respiratory tract infection, latent TB, abnormal liver function test, lower respiratory tract infection and UTI INX: infusion-related reaction, latent TB, upper respiratory tract infection, abnormal liver function test, UTI and lower respiratory tract infection Serious TEAEs: CT-P13: 13.9% INX: 10.3% Serious TEAEs related to treatment CT-P13: 7.6% INX: 4.7% One death in INX group; not considered related to treatment	The 54-week findings confirm those previously reported at week 30 [36] CT-P13 and INX were comparable in terms of efficacy (including radiographic progression) and immunogenicity up to week 54 The safety profile of CT-P13 was similar to that of INX

(continued)

Table 1 Continued

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
Yoo *et al.* [23] PLANETRA study switching extension to week 102	Phase III, open-label, extension study RA patients[a] CT-P13 (n = 302) INX (n = 304) for 54 weeks then CT-P13 maintenance (n = 158) or switch to CT-P13 (n = 144) for up to 102 weeks	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 12.5–25 mg/wk + folic acid ⩾5 mg/wk to week 54 then CT-P13/MTX/folic acid as above (weeks 64–102)	ACR20 response rate CT-P13 maintenance: 71.7% CT-P13 switch: 71.8% (95% CI: −10, 10) ACR50 response rate CT-P13 maintenance: 48.0% CT-P13 switch: 51.4% ACR70 response rate CT-P13 maintenance: 24.3% CT-P13 switch: 26.1% Mean improvement in DAS28/CRP CT-P13 maintenance: −2.40 CT-P13 switch: −2.48 Good EULAR response (CRP) CT-P13 maintenance: 40.1% CT-P13 switch: 44.4%	ADAs at week 78 CT-P13 maintenance: 44.7% CT-P13 switch: 46.2% ADAs at week 102 CT-P13 maintenance: 40.3% CT-P13 switch: 44.8%	Overall TEAEs CT-P13 maintenance: 53.5% CT-P13 switch: 53.8% TEAEs related to treatment CT-P13 maintenance: 22.0% CT-P13 switch: 18.9% Most frequently reported TEAEs related to treatment CT-P13 maintenance: infusion-related reaction, latent TB, upper respiratory tract infection, lower respiratory tract infection, UTI, bursitis CT-P13 switch: infusion-related reaction, latent TB, lower respiratory tract infection, abnormal liver function test, upper respiratory tract infection, UTI, urticaria Serious TEAEs CT-P13 maintenance: 7.5% CT-P13 switch: 9.1% Serious TEAEs related to treatment CT-P13 maintenance: 1.3% CT-P13 switch: 2.8% No deaths	Comparable efficacy and tolerability were observed in patients who switched from INX to CT-P13 for an additional year and in those who had long-term treatment with CT-P13 for 2 years
CT-P13 *vs* reference infliximab (INX): Japanese pharmacokinetic efficacy and safety studies in patients with RA						
Takeuchi *et al.* [21] Japanese study to week 54	Phase I/II, randomized, double-blind, multicenter, parallel-group study Japanese RA patients[a] CT-P13 (n = 50) INX (n = 51)	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 6–16 mg/wk + folic acid ⩾5 mg/wk	CT-P13/INX ratio (95% CI) in ADA-ve patients at week 14 AUC: 111.62% (100.24, 124.29) C_{max}: 104.09% (92.12, 117.61) ACR20 response rate CT-P13: 64.0% INX: 49.0% ACR50 response rate CT-P13: 50.0% INX: 31.4% ACR70 response rate CT-P13: 42.0% INX: 13.7%* Mean improvement in CDAI CT-P13: −17.4 INX: −13.7 Mean improvement in SDAI CT-P13: −18.4 INX: −14.1 Mean improvement in DAS28/CRP CT-P13: −2.1 INX: −1.4 Good/moderate EULAR response (CRP) CT-P13: 76.0% INX: 62.7% *P = 0.002	ADAs at week 14 CT-P13: 19.6% INX: 15.1% ADAs at week 30 CT-P13: 48.4% INX: 48.2%	Overall TEAEs CT-P13: 88.2% INX: 86.8% Most frequently reported TEAEs related to treatment CT-P13: abnormal hepatic function, nasopharyngitis, infusion-related reaction, upper respiratory tract infection, rash INX: abnormal hepatic function, nasopharyngitis, infusion-related reaction, eczema, rash Serious TEAEs CT-P13: 15.7% INX: 15.1%	CT-P13 and INX were pharmacokinetically equivalent and comparable in efficacy and safety when administered for 54 weeks in Japanese patients with RA

(continued)

Table 1 Continued

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
Tanaka *et al.* [24] Japanese switching extension study to week 134	Phase I/II open-label, single-arm, multicenter, extension study RA patients[a] CT-P13 (n = 50) INX (n = 51) 54 weeks then CT-P13 maintenance (n = 38) or switch to CT-P13 (n = 33) up to week 134	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 6–16 mg/wk + folic acid ⩾5 mg/wk to week 54 then CT-P13/MTX/folic acid as above (weeks 64–104); CT-P13 dose increase allowed to 10 mg/wk	ACR20 response rate CT-P13 maintenance: 78.4% CT-P13 switch: 62.5% ACR50 response rate CT-P13 maintenance: 70.3% CT-P13 switch: 53.1% ACR70 response rate CT-P13 maintenance: 54.1% CT-P13 switch: 40.1% Mean improvement in DAS28/ESR CT-P13 maintenance: 3.17 CT-P13 switch: 3.96	ADAs at week 110 CT-P13 maintenance: 11.8% CT-P13 switch: 21.7% ADAs at week 134 CT-P13 maintenance: 15.6% CT-P13 switch: 17.4%	Overall TEAEs CT-P13 maintenance: 89.5% CT-P13 switch: 87.9% Most frequently reported TEAEs related to treatment CT-P13 maintenance: nasopharyngitis, upper respiratory tract inflammation, herpes zoster, rash CT-P13 switch: nasopharyngitis, infusion-related reaction and osteoporosis Serious TEAEs CT-P13 maintenance: 5.3% CT-P13 switch: 12.1%	CT-P13 was well tolerated with persistent efficacy in Japanese patients with RA who maintained treatment after 54 weeks and in patients who switched to CT-P13 after 54 weeks of INX treatment
CT-P13 *vs* reference infliximab (INX): pharmacokinetic, efficacy and safety studies in patients with AS						
Park *et al.* [19] PLANETAS study at week 30	Phase I, randomized, double-blind, multicenter, multinational, parallel-group study AS patients CT-P13 (n = 125) INX (n = 125)	5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/NSAIDs allowed	CT-P13/INX ratio (95% CI) AUC: 104.5% (94–116) C_{max}: 101.5% (95–109) ASAS20 response rate CT-P13: 70.5% INX: 72.4% (95% CI: 0.51, 1.62) ASAS40 response rate CT-P13: 51.8% INX: 47.4% (95% CI: 0.70, 2.00) Mean change in ASDAS-CRP CT-P13: −1.8 INX: −1.7 Median change in BASDAI score CT-P13: −3.1 INX: −2.5 Median change in BASFI score CT-P13: −2.6 INX: −2.2 Median change in BASMI score CT-P13: −1.0 INX: −1.0 Median change in chest expansion score (cm) CT-P13: +0.5 INX: +0.5	ADAs at week 14 CT-P13: 9.1% INX: 11% ADAs at week 30 CT-P13: 27.4% INX: 22.5%	Overall TEAEs CT-P13: 64.8% INX: 63.9% Most frequently reported TEAEs related to treatment CT-P13: increased ALT and AST, latent TB, urinary tract infection, serum creatine phosphokinase elevation, γ-glutamyltransferase elevation INX: increased ALT and AST, γ-glutamyltransferase elevation, latent TB Serious TEAEs CT-P13: 4.8% INX: 6.4% No deaths	The PK profiles of CT-P13 and INX were equivalent in patients with AS. CT-P13 was well tolerated, with an efficacy and safety profile comparable to that of INX up to week 30
Park *et al.* [25] PLANETAS study extension to week 54	Phase I, randomized, double-blind, multicenter multinational, parallel-group study AS patients CT-P13 (n = 125) INX (n = 125)	5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/NSAIDs allowed	ASAS20 response rate CT-P13: 67.0% INX: 69.4% (95% CI: 0.50, 1.59) ASAS40 response rate CT-P13: 54.7% INX: 49.1% (95% CI: 0.73, 2.15) ASAS partial remission CT-P13: 19.8% INX: 17.6% Mean change in ASDAS-CRP score CT-P13: −1.7 INX: −1.7 Median change in BASDAI score CT-P13: −3.1 INX: −2.8	ADAs at week 30 CT-P13: 19.5% INX: 23.0%	Overall TEAEs CT-P13: 74.2% INX: 67.2% TEAEs related to treatment CT-P13: 50.0% INX: 51.6% Most frequently reported TEAEs related to treatment CT-P13: abnormal liver function test, upper respiratory tract infection, infusion-related reaction, latent TB INX: abnormal liver function test, infusion-related reaction, upper respiratory tract infection, latent TB Serious TEAEs CT-P13: 7.8% INX: 6.6%	The 54-week findings confirm those previously reported at week 30 CT-P13 and INX have highly comparable efficacy, safety and immunogenicity and PK profiles up to week 54

(continued)

Table 1 Continued

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
			Median change in BASFI score CT-P13: −2.9 INX: −2.7 Median change in BASMI score CT-P13: −1.1 INX: −0.9 Median change in chest expansion score (cm) CT-P13: +0.7 INX: +0.9		Serious TEAEs related to treatment CT-P13: 3.1% INX: 4.1% Two deaths (one in each treatment arm); both car accidents and not considered related to study treatment	
Park *et al.* [26] PLANETAS study switching extension to week 102	Phase I, open-label, extension study AS patients CT-P13 (n = 125) INX (n = 125) for 54 weeks then CT-P13 maintenance (n = 88) or switch to CT-P13 (n = 86) up to week 102	5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/NSAIDs allowed then CT-P13/glucocorticoids/NSAIDs as above (weeks 62–102)	ASAS20 response rate CT-P13 maintenance: 80.7% CT-P13 switch: 76.9% (95% CI: 0.58, 2.70) ASAS40 response rate CT-P13 maintenance: 63.9% CT-P13 switch: 61.5% (95% CI: 0.57, 2.07) ASAS partial remission CT-P13 maintenance: 19.3% CT-P13 switch: 23.1% (95% CI: 0.37, 1.72) Mean ASDAS-CRP score CT-P13 maintenance: −1.86 CT-P13 switch: −1.97 Mean change in BASDAI score CT-P13 maintenance: −3.19 CT-P13 switch: −3.23 Mean change in BASFI score CT-P13 maintenance: −3.10 CT-P13 switch: −3.25 Mean change in BASMI score CT-P13 maintenance: −2.4 CT-P13 switch: −2.6	ADAs at week 78 CT-P13 maintenance: 23.3% CT-P13 switch: 29.8% ADAs at week 101 CT-P13 maintenance: 23.3% CT-P13 switch: 27.4%	Overall TEAEs CT-P13 maintenance: 48.9% CT-P13 switch: 71.4% TEAEs related to treatment CT-P13 maintenance: 22.2% CT-P13 switch: 39.3% Most frequently reported TEAEs related to treatment CT-P13 maintenance: infusion-related reactions, abnormal liver function test, upper respiratory tract infection, latent TB, elevated serum creatine kinase, lower respiratory tract infection CT-P13 switch: infusion-related reactions, abnormal liver function test, latent TB, back pain, upper respiratory tract infection Serious TEAEsCT-P13 maintenance: 4.5%CT-P13 switch: 4.7% Serious TEAEs related to treatment CT-P13 maintenance: 2.3% CT-P13 switch: 2.3%	This is the first study to show that switching from INX to its biosimilar CT-P13 is possible without negative effects on safety or efficacy in patients with AS
CT-P13 *vs* reference infliximab (INX): observational studies in patients with spondyloarthritis/rheumatic disease						
Benucci *et al.* [27] 6-month, real-life observational study	Observational Italian study in patients with spondyloarthritis (n = 41) switched from INX (median treatment duration 124.5 months) to CT-P13 for 6 months	No dosage details provided (within label restrictions)	Median BASDAI Baseline: 2.73 ± 1.5 After 6 months: 2.6 ± 1.3 P = 0.27 BASFI Baseline: 2.34 ± 1.3 After 6 months: 2.17 ± 1.2 P = 0.051 ASDAS-CRP Baseline: 1.35 ± 0.3 After 6 months: 1.28 ± 0.2 P = 0.92 DAS28-CRP Baseline: 2.66 ± 0.67	INX levels μg/ml Baseline: 4.22 ± 2.89 After 6 months: 4.84 ± 2.86 P = 0.80 Anti-INX antibody levels ng/ml Baseline: 27.76 ± 17.13 After 6 months: 27.27 ± 17.28 P = 0.98	AEs were similar during CT-P13 and prior INX treatment One patient withdrew due to an AE	Switching from INX to CT-P13 was not associated with any statistically significant difference in efficacy, AEs or ADA levels

(continued)

Table 1 Continued

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
			After 6 months: 2.67 ± 0.35 P = 0.24 MASES Baseline: 0.35 ± 0.7 After 6 months: 0.17 ± 0.4 P = 0.08 VAS pain Baseline: 18 ± 14.7 After 6 months: 16.7 ± 11.3 P = 0.55 Morning stiffness Baseline: 7.2 ± 6.9 After 6 months: 5.8 ± 6 P = 0.02			
Nikiphorou *et al.* [28] Clinical experience in routine rheumatology clinic	Observational Italian study in patients with rheumatic disease (n = 39) switched from INX (median treatment duration 4.1 years) to CT-P13	Same dose and frequency as prior INX; 31 patients on concomitant MTX	Mean AUC for: Pain During INX: 26 During CT-P13: 24 INX *vs* CT-P13, P = 0.36 Fatigue During INX: 28 During CT-P13: 24 INX *vs* CT-P13, P = 0.079 PtGlob During INX: 26 During CT-P13: 24 INX *vs* CT-P13, P = 0.24 PtAct During INX: 21 During CT-P13: 24 INX *vs* CT-P13, P = 0.25 HAQ During INX: 0.58 During CT-P13: 0.61 INX *vs* CT-P13, P = 0.44 DrGlob During INX: 5.9 During CT-P13: 3.8 INX vs CT-P13, P = 0.18	Three patients had ADAs to INX before CT-P13 was initiated and discontinued	One patient had neurofibromatosis and one patient had latent TB reactivation	The clinical effectiveness of CT-P13 in both patient-reported outcomes and disease activity was comparable to INX during the first year of switching, with no immediate safety signals
SB2 *vs* reference infliximab (INX): multinational efficacy and safety study in patients with RA						
Choe *et al.* [35] Study to week 30	Phase III, randomized, double-blind multicenter, multinational, parallel-group study RA patients[a] SB2 (n = 290) INX (n = 293)	3 mg/kg IV SB2 or INX, weeks 0, 2, 6 then q8wks + MTX 10–25 mg/wk + folic acid ⩾5 mg/wk allowed Dose increase allowed from week 30—by 1.5 mg/wk to max 7.5 mg/wk	ACR20 response rate SB2: 64.1% INX: 66.0% (95% CI: −10.26, 6.51) ACR50 response rate SB2: 35.5% INX: 38.1% (95% CI: −10.69, 6.43) ACR70 response rate SB2: 18.2% INX: 19.0% (95% CI: −7.26, 6.75)	ADAs at week 30 SB2: 55.1% INX: 49.7%	Overall TEAEs SB2: 57.6% INX: 58.0% TEAEs related to treatment SB2: 21.4% INX: 20.1% Most frequently reported TEAEs related to treatment SB2: increased alanine aminotransferase, latent TB, headache, RA, nasopharyngitis	Results demonstrate the equivalence of efficacy between SB2 and INX, as well as the comparability in safety, immunogenicity and PK profiles

(continued)

Table 1 Continued

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
			Mean improvement in CDAI SB2: −23.3 INX: −23.1 Mean improvement in SDAI SB2: −23.5 INX: −23.6 Mean improvement in DAS28/ESR SB2: −2.3 INX: −2.3 % achieving LDAS (DAS28 ⩽2.6 to ⩽3.2) SB2: 11.1% INX: 9.8% % achieving remission (DAS28 ⩽2.6) SB2: 14.6% INX: 15.9% Good and moderate EULAR response (CRP) SB2: 25.7 and 58.1%, respectively INX: 25.7 and 54.7%, respectively		INX: latent TB, nasopharyngitis, headache, bronchitis, RA Serious TEAEs SB2: 9.0% INX: 8.9% One death in INX group (heart failure)	
SB4 *vs* reference etanercept (ENT): multinational efficacy and safety study in patients with RA						
Emery *et al.* [44] Study to week 24	Phase III, randomized, double-blind, multicenter, multinational, parallel-group study RA patients[a] SB4 (n = 299) ETN (n = 297)	50 mg/wk SC SB4 or ENT + MTX 10–25 mg/wk + folic acid 5–10 mg/wk	ACR20 response rate SB4: 78.1% ENT: 80.3% (95% CI: −9.41, 4.98) ACR50 response rate SB4: 46.6% ENT: 42.3% (95% CI: −3.92, 13.49) ACR70 response rate SB4: 25.5% ENT: 22.6% (95% CI: −4.47, 10.51) Mean improvement in DAS28-ESR SB4: −2.6 ENT: −2.5 % achieving LDAS (DAS28 ⩽3.2) SB4: 31.4% ENT: 27.6% % achieving remission (DAS28 ⩽2.6) SB4: 16.7% ENT: 16.2% Good and moderate EULAR response (CRP) SB4: 32.1 and 55.1%, respectively ENT: 29.8 and 58.5%, respectively	ADAs at week 30 SB4: 0.7% ENT: 13.1%** **$P < 0.001$ Most appeared early (weeks 28) and most disappeared after week 12	Overall TEAEs SB4: 55.2% ENT: 58.2% TEAEs related to treatment SB4: 27.8% ENT: 35.7% Most frequently reported TEAEs related to treatment SB4: upper respiratory tract infection, increased alanine aminotransferase, nasopharyngitis, headache ENT: injection-site erythema, upper respiratory tract infection, nasopharyngitis, increased alanine aminotransferase Serious TEAEs SB4: 4.3% ENT: 4.3% One death in SB4 group (cardiorespiratory failure); not considered related to drug	SB4 was shown to be equivalent with ENT in terms of efficacy. SB4 was well tolerated, with a lower immunogenicity profile. The safety profile of SB4 was comparable to that of ETN

/

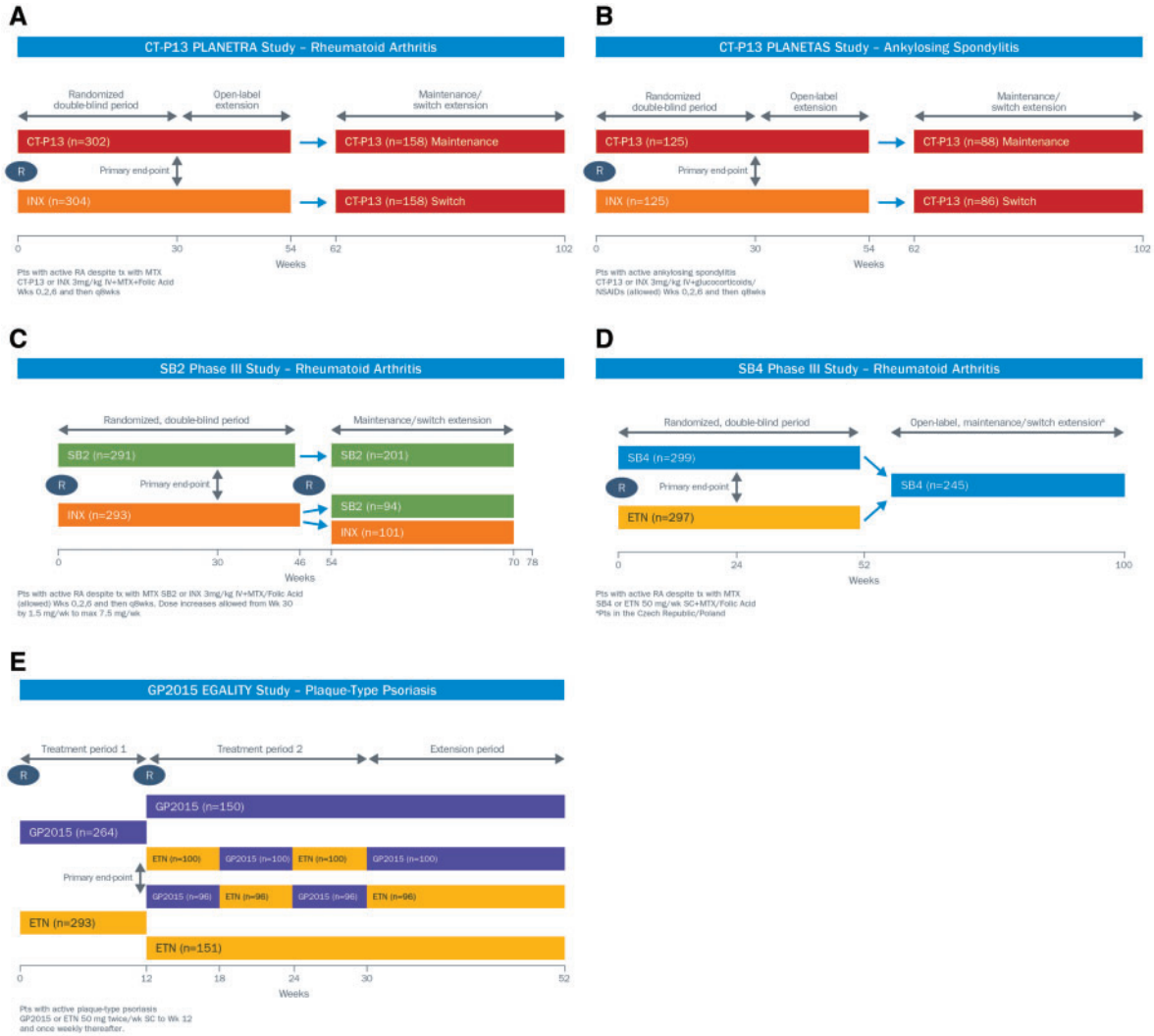
(continued)

Table 1 Continued

References	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
GP2015 *vs* reference etanercept (ENT): multinational efficacy and safety study in patients with plaque psoriasis						
Griffiths *et al.* [51] EGALITY study	Phase III, randomized, double-blind, multicenter, multinational, parallel-group study Mild to moderate plaque-type psoriasis patients[b] GP2015 (n = 264) ETN (n = 267) to week 12 then GP2015 maintenance (n = 150), GP2015 switch to ETN (n = 100), ETN maintenance (n = 151) or ETN switch to GP2015 (n = 96) from weeks 12 to 30 then GP2015 maintenance (n = 140), GP2015 switch to ETN (n = 95), ETN maintenance (n = 142) or ETN switch to GP2015 (n = 90) from weeks 12 to 30	50 mg twice/wk SC GP2015 or ENT to week 12 then 50 mg/wk SC GP2015 or ENT once weekly	PASI75 response rate at week 12 GP2015: 73.4% ENT: 75.7% (95% CI: −9.85, 5.30) Mean difference in PASI score to week 12 −0.64 (95% CI: −3.47, 2.20) Proportion of IGA responders GP2015: 59.4% ENT: 55.6% PASI 50/75/90 response rate at week 52[c] Continued GP2015 ≡ continued ENT Pooled continued ≡ pooled switched Observed PASI score at week 52[c] Continued GP2015 ≡ continued ENT Pooled continued ≡ pooled switched % change in PASI score at week 52[c] Continued GP2015 ≡ continued ENT Pooled continued ≡ pooled switched	ADAs Continued GP2015: 0.0% Continued ENT: 1.9% Switched GP2015: 0.0% Switched ENT: 1.1%	Overall TEAEs at week 54 Continued GP2015: 59.8% Continued ENT: 57.3% Switched GP2015: 61.0%Switched ENT: 59.4% TEAEs related to treatment Continued GP2015: 20.7% Continued ENT: 19.3% Switched GP2015: 22.0% Switched ENT: 20.8% Serious TEAEs Continued GP2015: 4.3% Continued ENT: 4.1% Switched GP2015: 6.0% Switched ENT: 6.3% One death in the ENT group in treatment period (cardiopulmonary failure); not considered related to drug	This study demonstrated the equivalent efficacy and comparable safety and immunogenicity of GP2015 and ENT in patients with moderate to severe chronic plaque-type psoriasis

Data taken from references [19–28, 35, 44, 51]. [a]Patients enrolled with an inadequate response to prior treatment with MTX. [b]Patients enrolled had previously received or were eligible for phototherapy or systemic psoriasis therapy. Patients with a 50% improvement in PASI (PASI50) at week 12 were re-randomized to continue the same treatment on a once-weekly dosing schedule or to undergo a sequence of three treatment switches between GP2015 and ETN until week 30. Thereafter, patients continued treatment with the product that they had been assigned to last, up to week 52. [c]Raw data not provided. ≡: overall equivalence; ALT: alanine transaminase; ADA: antidrug antibody; AE: adverse event; ASAS: Assessment in AS; AST: aspartate transaminase; AUC: area under the curve; CDAI: Clinical Disease Activity Index; C_{max}: maximum plasma drug concentration; DrGlob: Doctor Global Assessment Activity Score; ETN: etanercept; IGA: Investigator's Global Assessment; INX: innovator infliximab; LDAS: low Disease Activity Score; MASES: Maastricht AS Enthesitis Score; PASI: Psoriasis Area and Severity Index; PK: pharmacokinetics; ptACT: patient disease activity; ptGlob: patient global estimate; q8wk: every 8 weeks; SDAI: Simple Disease Activity Index; TEAE: treatment-emergent adverse event; TB: tuberculosis; UTI: urinary tract infection; VAS: Visual Analogue Scale.

FIG. 1 Study design of key studies on biosimilars



(**A**) CT-P13 PLANETRA study—RA. (**B**) CT-P13 PLANETAS study—AS. (**C**) SB2 phase III study—RA. (**D**) SB4 phase III study—RA and (**E**) GP2015 EGALITY study plaque-type psoriasis. Data taken from [19, 20, 22, 23, 25, 26, 35–37, 44–46, 51].

Activity Index and Simplified Disease Activity Index, or the proportion of patients who achieved low disease activity or remission based on the DAS28 (Table 1) [20]. A total of 455 patients in PLANETRA were treated up to week 54 [22]. Longer term, at week 54, the proportion of patients achieving ACR20, ACR50 and ACR70 responses continued to be similar in both treatment groups, and improvements in disease activity, as measured by mean changes from baseline in DAS28, Clinical Disease Activity Index and Simplified Disease Activity Index scores, were also maintained with each regimen [22] (Table 1). Results from the PLANETRA extension study (n = 302), which assessed the efficacy and safety of switching from reference infliximab to CT-P13 or continuing CT-P13 in patients who had completed 54 weeks of treatment, reported that response rates were maintained and did not significantly differ in the switch and maintenance groups up to 102 weeks [23] (Table 1). Further support for the comparable efficacy of CT-P13 and reference infliximab in RA comes from a small phase I/II study in Japanese patients (n = 101), in which patients were treated with either agent at a dose of 3 mg/kg with MTX supplementation [21]. The proportions of patients achieving ACR20 response at weeks 14, 30 and 54 were not significantly different between CT-P13 and reference infliximab. Furthermore, there were no significant between-group differences in ACR50, ACR70 or the EULAR response rates at any time point, with the exception of the ACR70 response rate at week 54 [21] (Table 1). Results from the extension phase of this study (n = 72), which assessed the safety and efficacy of switching from reference infliximab to CT-P13 or continuing CT-P13 in patients who had completed 54 weeks of treatment, reported that ACR response rates improved in both the

switch and maintenance groups up to week 134 [24] (Table 1).

The efficacy of CT-P13 for the treatment of AS was investigated in the randomized, double-blind, multicenter PLANETAS trial, in which patients with active AS were treated with either CT-P13 or reference infliximab at a dose of 3 mg/kg (n = 250) (Fig. 1B) [19]. Although the primary end point of the study was to demonstrate pharmacokinetic equivalence between CT-P13 and reference infliximab, efficacy endpoints were also assessed. Improvements in the signs and symptoms of AS did not significantly differ between CT-P13 and reference infliximab, as assessed by the Assessment in AS (ASAS) 20 and ASAS40 response rates after 30 or 54 weeks of treatment [19, 25] (Table 1). There were also no marked between-group differences in improvements in other efficacy measures assessing disease activity, including ASDAS-CRP level, BASDAI, spinal mobility (BASMI) and physical function (BASFI) [19, 25] (Table 1). Results from the PLANETAS extension study (n = 174), which assessed the efficacy and safety of switching from reference infliximab to CT-P13 or continuing CT-P13 in patients who had completed 54 weeks of treatment, demonstrated that response rates were maintained and did not significantly differ in the switch and maintenance groups up to 102 weeks (Table 1) [26].

The efficacy of switching to CT-P13 from reference infliximab has also been examined in a range of rheumatic and inflammatory diseases. Results from a 6-month, real-life, observational study in patients with spondyloarthritis (n = 41) reported that switching from reference infliximab to CT-P13 was not associated with any statistically significant differences in efficacy, as assessed by the median BASDAI, BASFI, ASDAS, DAS28, Maastricht Ankylosing Spondylitis Enthesitis and Visual Analogue Scale pain scores, whereas the median duration of morning stiffness significantly decreased [27] (Table 1). Likewise, results from a prospective, observational study in 39 consecutive patients with established rheumatic diseases (RA, AS, PsA and JIA) who were switched to CT-P13 after a mean of 4.1 years on reference infliximab reported that the clinical effectiveness of CT-P13 in both patient-reported outcomes and disease-activity measures was comparable to reference infliximab during the first year of switching [28] (Table 1). Several registries and post-marketing studies are ongoing to evaluate CT-P13 in several indications and to further assess clinical outcomes following a switch from reference infliximab to CT-P13. For example, data from the DANBIO registry has provided support for the efficacy of switching from reference infliximab to CT-P13 in 802 patients with inflammatory arthritis (RA, PsA and axial spondyloarthritis). Three months after switching from reference infliximab to CT-P13, disease activity was largely unchanged in most patients [29]. Likewise, results from the NOR-SWITCH trial, a 52-week, randomized, double-blind, non-inferiority phase IV trial, which was funded by the Norwegian government, demonstrated that switching patients who were stable on reference infliximab to CT-P13 was not inferior to continued treatment with reference infliximab in adult patients (n = 481) with a diagnosis of five inflammatory diseases: RA, PsA, Crohn's disease, ulcerative colitis and chronic plaque psoriasis [30]. In July 2015, the Dutch authorities began funding a similar trial (BIO-SWITCH) to study the effects on efficacy, safety and immunogenicity of switching treatment from reference infliximab to CT-P13 in patients with RA, spondyloarthritis or PsA. Results are expected in 2017 [31].

A proportion of patients with RA and AS tested positive for antidrug antibodies (ADAs) at week 54 after treatment with CT-P13 and reference infliximab in PLANETRA (41.1 and 36.0%, respectively) [22], and PLANETAS (19.5 and 23.0%, respectively) [25] (Table 1). At week 102, the proportion of ADA-positive patients was similar in the switch and maintenance groups of the PLANETRA extension (44.8 and 40.3%, respectively) [23] and PLANETAS extension (27.4 and 23.3%, respectively) [26] (Table 1). In both studies, the vast majority of patients with a positive ADA result were also positive for neutralizing antibodies. In support of these findings, results from real-world studies in patients with rheumatic disease have reported that switching from reference infliximab to CT-P13 was not associated with an increase in immunogenicity [27, 28].

CT-P13 was generally well tolerated for up to 54 weeks of treatment in patients with RA [22] and AS [25], with a tolerability profile similar to that of reference infliximab. Overall, treatment-related adverse events (AEs) occurred in 43.7% of CT-P13 patients and 45.0% of reference infliximab patients in PLANETRA [22], and 50.0 and 51.6%, respectively, in PLANETAS [25] (Table 1). The majority of AEs were of mild to moderate intensity, with the most frequently reported treatment-related AEs being abnormal liver function tests, infusion-related reactions, latent tuberculosis and upper respiratory tract infection [22, 25]. Serious treatment-related AEs occurred in 7.6% of CT-P13 patients and 4.7% of reference infliximab patients in PLANETRA [22], and 3.1 and 4.1%, respectively, in PLANETAS [25] (Table 1). Although regulatory evaluation highlighted a numerical imbalance in serious AEs in PLANETRA, with a higher incidence of serious infections, including latent tuberculosis being noted for CT-P13, the numbers were low and the EMA considered the difference to be a chance finding [15]. According to the open-label extensions of PLANETRA and PLANETAS, CT-P13 continued to be well tolerated in the longer term, with switching from reference infliximab to CT-P13 at week 54 having no detrimental effect on safety over a further 48 weeks of treatment (Table 1) [23, 26]. Real-world studies have also reported that switching from reference infliximab to CT-P13 was generally well tolerated, with no safety signals, in patients with rheumatic diseases [24, 28] (Table 1).

SB2

SB2 (Flixabi®) is an infliximab biosimilar that has recently received marketing authorization in the EU for use in the treatment of adult patients with RA, PsA, psoriasis,

ulcerative colitis or Crohn's disease and young people with ulcerative colitis or Crohn's disease, as for reference infliximab [32]. Overall, the physicochemical and biologic characteristics (including TNF binding and TNF-α neutralization activities and Fc-related biologic activities, such as ADCC, complement-dependent cytotoxicity, neonatal Fc receptor binding, C1q binding and Fc gamma receptor binding) for SB2 have been shown to be similar to those of reference infliximab [32]. Although a few small differences in physicochemical attributes were observed in terms of charged glycans, charge variants and high molecular mass aggregates between SB2 and reference infliximab, evidence from the related literature, structure–activity relationship studies and comparative biologic assays showed that these differences were unlikely to be clinically meaningful [33].

Evidence of pharmacokinetic equivalence between SB2 and two reference infliximab products sourced from the EU and the USA was provided by a randomized, parallel, three-arm, single-blind study of 159 healthy volunteers over 10 weeks [34]. Following administration of a single dose of 5 mg/kg, the 90% CIs for the geometric least squares mean ratios for the primary pharmacokinetic parameters [AUC from time zero to infinity (AUC_{inf}), AUC from time zero to the last quantifiable concentration (AUC_{last}) and C_{max}] for each comparison were within the predefined equivalence margin (e.g. 80–125%) [34].

The equivalence of SB2 and reference infliximab was subsequently confirmed in a phase III, randomized, double-blind trial of 584 patients with RA, which consisted of a 54-week main study and an additional 24-week transition (switching) study [35–37] (Fig. 1C). Patients with active disease, despite prior treatment with MTX, received SB2 or reference infliximab at a dose of 3 mg/kg in conjunction with MTX for up to 30 weeks. This trial met its primary efficacy end point for equivalence of efficacy as the 95% CI for the difference in the ACR20 response rate at week 30 was contained within the predefined equivalence margin (e.g. ±15%) in the per-protocol set (SB2, 64.1%; reference infliximab, 66.0%; 95% CI: −10.26, 6.51) [35]. Other efficacy endpoints, including ACR50/70, DAS28 and EULAR response, were also similar in both treatment groups at week 30 [35] (Table 1). A total of 452 patients completed 54 weeks of treatment (available as an abstract) [36]. At week 54, patients receiving SB2 or reference infliximab demonstrated similar ACR20 response rates (50.7 *vs* 52.6%, respectively), ACR50 response rates (32.1 *vs* 29.7%, respectively) and ACR70 response rates (18.3 *vs* 17.7%, respectively) [36]. Likewise, other secondary efficacy parameters at week 54, such as DAS28 and EULAR response rates, were also similar between the two treatment groups. Radiographic damage, as assessed by the change in modified total sharp score from baseline to week 54, was comparable between the two treatment groups (mean change: 0.38 for SB2 *vs* 0.37 for reference infliximab) [36]. At week 54, patients receiving reference infliximab were randomized to either continue treatment with infliximab (n = 101) or to switch to SB2 (n = 94), whereas those previously treated with SB2 continued to receive SB2 (n = 201), but followed the randomization procedure to maintain blinding (available as an abstract) [37]. Assessments up to week 78 demonstrated that ACR response rates were sustained and comparable across treatment groups [37].

A similar proportion of patients with RA tested positive for ADAs at week 30 after treatment with SB2 and reference infliximab (55.1 and 49.7%, respectively; P = 0.212; Table 1) [35]. Likewise, at week 54, there was no significant difference in the incidence of ADAs following treatment with SB2 and reference infliximab (62.4 and 57.5%, respectively; P = 0.270) [36]. At week 78, ADAs were documented for 45.7–53.6% of patients; among patients with overall negative ADA results up to week 54, newly developed ADAs were noted in 14.6% of patients who transitioned from reference infliximab to SB2, 14.9% of patients who continued with reference infliximab and 14.1% of patients who continued with SB2 at week 78 [37]. SB2 was generally well tolerated in patients with RA, with a tolerability profile similar to that of reference infliximab [35–37]. At week 30, the incidence of treatment-emergent AEs was comparable between SB2 and reference infliximab (57.6 and 58.0%, respectively) [35]. The majority of AEs were of mild to moderate intensity, with the most frequently reported being latent tuberculosis, increased alanine aminotransferase levels and headache (Table 1). Similarly, at week 54, there was no significant difference in the incidence of treatment-emergent AEs following treatment with SB2 and reference infliximab (61.7 and 65.2%, respectively) [36]. At week 78, treatment-emergent AEs were documented for 36.2% of patients who transitioned from reference infliximab to SB2, 35.6% of patients who continued with reference infliximab and 40.3% of patients who continued with SB2 [37].

Etanercept biosimilars

Etanercept (Enbrel®) is an anti-TNF agent that is approved for use in adult patients with moderate-to-severe active and/or progressive RA, active and progressive PsA, severe active AS, severe non-radiographic axial spondyloarthritis and severe plaque psoriasis, and in young people with JIA (polyarthritis, extended oligoarthritis, PsA and enthesitis-related arthritis) and severe plaque psoriasis [38]. To date, the etanercept (Enbrel®) biosimilar SB4 (Benepali®) has been approved for patients with rheumatic diseases in the EU. As of March 2017, an estimated 30 000 patients have been treated with SB4 in Europe [39].

SB4

SB4 (Benepali®) is an etanercept biosimilar that has been approved for use in the treatment of adult patients with RA, PsA, AS, non-radiographic axial spondyloarthritis and plaque psoriasis [40, 41]. Results from a large characterization study demonstrated that SB4 is highly similar to reference etanercept in physicochemical and biologic attributes, including TNR receptor-related binding and Fc-

related binding [42]. Although a few differences in quality were observed in terms of high molecular mass aggregate levels and impurity levels, these differences were sufficiently justified by the results of a structure–activity relationship study that showed that these differences did not negatively influence the key indicators of biologic activities of SB2 [42].

The comparability of the pharmacokinetics of SB4 and reference etanercept sourced from the EU (EU-E) and US (US-E) was determined in a randomized, single-blind, three-way, phase I study of 138 healthy male volunteers [43]. In each part, SB4 and reference etanercept were administered as a single 50 mg dose, and pharmacokinetics parameters were measured after 21 days; each treatment sequence (Part A: SB4 *vs* EU-E; Part B: SB4 *vs* US-E; Part C: EU-E *vs* US-E) was separated by a 28-day washout period. The geometric least squares mean ratios of AUC_{inf}, AUC_{last} and C_{max} were similar between the two treatments in each part: 99.04, 98.62 and 103.71% (Part A: SB4 *vs* EU-E); 101.09, 100.96 and 104.36% (Part B: SB4 *vs* US-E); and 100.51, 101.27 and 103.29% (Part C: EU-E *vs* US-E), respectively, and the corresponding 90% CIs were completely contained within the pre-specified bioequivalence interval (e.g. 80–125%) [43].

The equivalence of SB4 and reference etanercept was subsequently confirmed in a phase III, randomized, double-blind trial of 596 patients with RA, which consisted of a 52-week main study and an additional 48-week transition (switching) study (Fig. 1D) [44–46]. Patients with moderate to severe RA, despite prior treatment with MTX, received SB4 or reference etanercept at a dose of 50 mg every week in conjunction with MTX for up to 24 weeks. This trial met its primary efficacy end point for equivalence of efficacy as the 95% CI for the difference in the ACR20 response rate at week 24 was contained within the pre-defined equivalence margin (e.g. ±15%) in the per protocol set (SB4, 78.1%; reference etanercept, 80.3%; 95% CI: −9.41, 4.98; Table 1). Other efficacy endpoints, including ACR50/70, were also comparable in both treatment groups at week 24 [44] (Table 1). A total of 505 patients completed 52 weeks of treatment (available as an abstract) [45]. At week 52, patients receiving SB4 or reference etanercept demonstrated similar ACR20 response rates (70.2 *vs* 65.7%, respectively), ACR50 response rates (47.8 *vs* 42.1%, respectively) and ACR70 response rates (30.4 *vs* 24.6%, respectively) [45]. Radiographic damage, as assessed by the change in modified total sharp score from baseline to week 54, was comparable between the two treatment groups (mean change: 0.45 for SB4 *vs* 0.74 for reference etanercept) [45]. At week 52, patients either continued to receive SB4 (n = 126) or switched from reference etanercept to SB4 (n = 119) (available as an abstract) [46]. Assessments up to week 100 demonstrated that ACR response rates were sustained and comparable across treatment groups [46].

The incidence of ADA development up to week 24 was significantly lower with SB4 compared with reference etanercept (0.7 *vs* 13.1%, respectively; $P < 0.001$; Table 1) [44]. Likewise, at week 54, the incidence of ADAs was also significantly lower with SB4 compared with reference etanercept (1.0 *vs* 13.2%; $P < 0.001$) [45]. The overall incidence of ADAs from weeks 52 to 100 was 0.8% in patients who continued with SB4 and 0.9% in patients who switched from reference etanercept to SB4 [46].

SB4 was generally well tolerated in patients with RA, with a tolerability profile similar to that of reference etanercept [44–46]. At week 24, the incidence of treatment-emergent AEs was comparable between SB4 and reference etanercept (55.2 and 58.2%, respectively; Table 1) [44]. The majority of AEs were of mild to moderate intensity, with the most frequently reported being upper respiratory tract infection, increased alanine aminotransferase levels, injection-site erythema and nasopharyngitis (Table 1). Serious treatment-related AEs occurred in 13 patients each in the SB4 and reference etanercept groups [44]. Similarly, at week 52, there was no significant difference in the incidence of treatment-emergent AEs following treatment with SB4 and reference infliximab (58.5 and 60.3%, respectively) [45]. The incidence of treatment-emergent AEs newly occurring from weeks 52 to 100 was 47.6% in patients who continued with SB4 and 48.7% in patients who switched from reference etanercept to SB4 [46].

Other etanercept biosimilars

A further etanercept biosimilar (GP2015) is under development by Sandoz. This agent has been approved for the same indications as reference etanercept in the USA [47], and a regulatory submission for its approval in the EU was made in December 2015 [48]. Results from an analytical and non-clinical comparability exercise confirmed that GP2015 and reference etanercept are comparable in regard to functional (target binding and anti-TNF-α biologic activity), pharmacokinetics and toxicological profiles. Furthermore, the pharmacodynamic biosimilarity of GP2015 and Enbrel® was confirmed in a well-established animal model of RA [TNF-α transgenic (Tg197) mouse] [49].

Evidence of pharmacokinetic equivalence between GP2015 and reference etanercept was provided by a randomized, two-sequence, two-period, cross-over study in healthy male subjects (n = 54) [50]. Following administration of either agent, at a single dose of 50 mg/kg, the mean serum concentration–time profiles were similar between GP2015 and reference etanercept. In addition, the 90% CIs of the geometric mean ratios for the primary endpoints [C_{max}, AUC from the time of the dosing and extrapolated to infinity ($AUC_{0\text{-}inf}$) and AUC from the time of dosing to the last measurable concentration ($AUC_{0\text{-}tlast}$)] were within the pre-defined equivalence margin (80–125%) [50].

The efficacy and safety of GP2015 were assessed in the randomized, double-blind EGALITY study, in which patients (n = 531) with moderate to severe chronic plaque-type psoriasis were treated with either GP2015 or reference etanercept [51]. The study consisted of four periods (Fig. 1E). In the first 12-week treatment period, patients received GP2015 or reference etanercept (50 mg twice weekly). In treatment period 2, patients who had achieved

at least a 50% improvement in Psoriasis Area and Severity Index (PASI) 50 from baseline at week 12 were re-randomized to either continue the same treatment on a once-weekly dosing schedule or to undergo a sequence of three treatment switches between GP2015 and reference etanercept at 6-weekly intervals until week 30. During the extension phase, patients continued to receive the same treatment received during the final 6 weeks of treatment period 2. This trial met its primary end point for equivalence of efficacy as the difference in PASI75 response rates at week 12 between GP2015 and reference etanercept was –2.3%, with the 95% CI (–9.85, 5.30) being well contained within the pre-defined equivalence margin (–18, 18) [51]. The main secondary end point, mean percentage change from baseline in PASI score at week 12, was similar between GP2015 and reference etanercept (Table 1). Likewise, other endpoints, including PASI50, 75 and 90 response rates at week 52, were comparable between the continued GP2015 and reference etanercept groups and between the pooled continued and pooled switched treatment groups [51] (Table 1).

ADAs, all non-neutralizing, were limited to five patients receiving reference etanercept during treatment period 1, and one patient in the switched reference etanercept group, who had been treated with GP2015 for 12 weeks at the time of the finding [51]. The incidence of treatment-emergent AEs up to week 52 was comparable between continued GP2015 and continued reference etanercept groups and was not impacted by switching (Table 1). The incidence of serious AEs and treatment-related TEAEs was similar between the two continued treatment groups and between the two switched treatment groups [51] (Table 1).

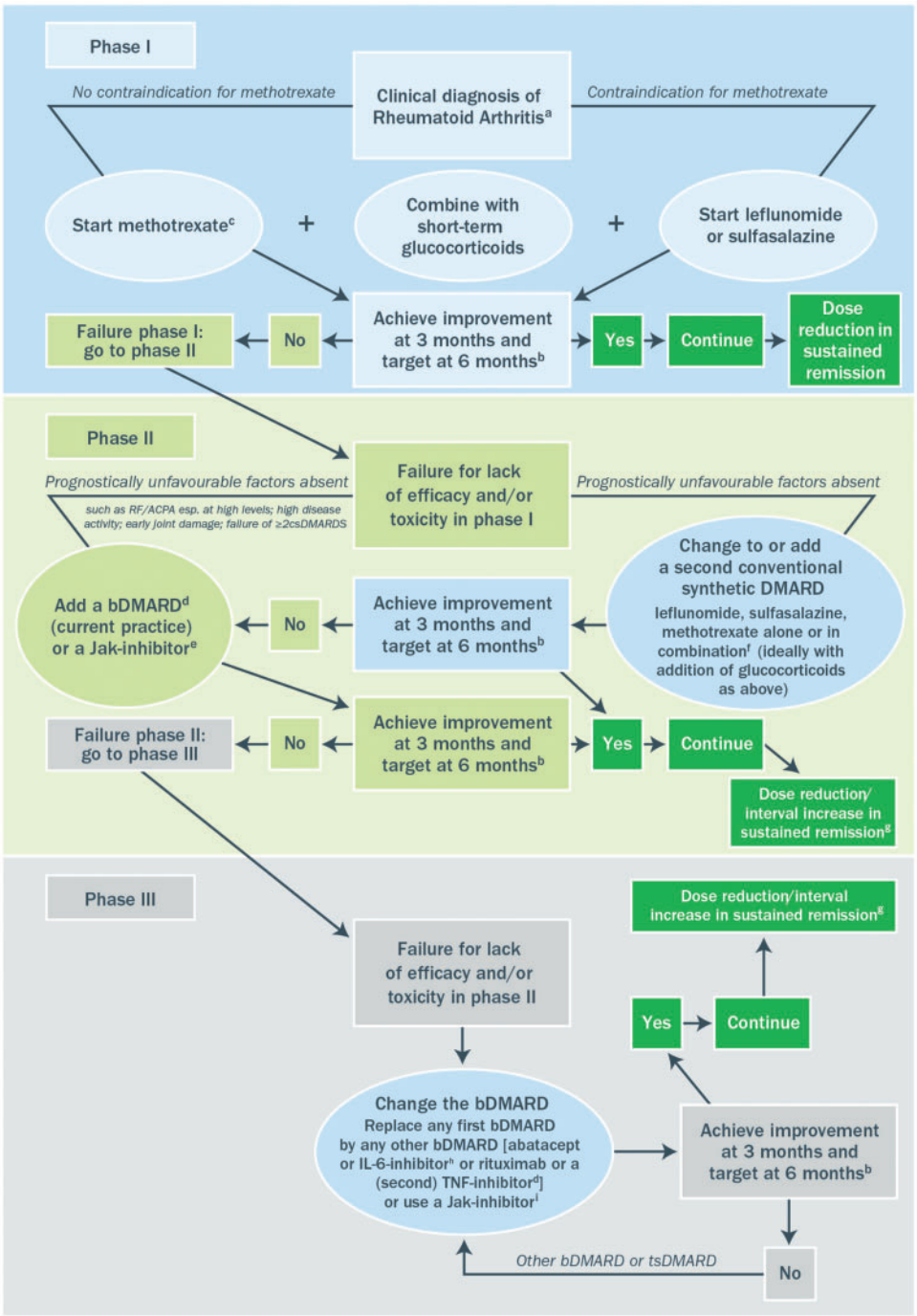
How should biosimilars fit into current clinical practice?

The two reference anti-TNF agents (infliximab and etanercept) and their biosimilars are indicated for use in patients with rheumatic diseases (plus psoriasis and IBD), generally following lack of response or intolerance to first-line or standard therapy, the exception being their use in patients with severe active and progressive RA, in which they are approved for first-line use [14, 16, 17, 38, 40, 52]. Guidelines on the use of biologic agents for patients with rheumatic diseases follow a similar theme [2, 3, 5–7]. For example, current European guidelines on the treatment of RA, which were updated in 2016, provide due consideration to biosimilars as part of the bDMARD treatment algorithm [6]. In those patients who do not respond adequately to first-line treatment, when alternative treatment strategies such as a treat-to-target (or tight control) approach with combination conventional synthetic DMARDs (csDMARDs) [53–55] and the use of combination csDMARDs following inadequate response to csDMARD therapy [56, 57] have failed, or those patients who experience unacceptable toxicity within 6 months of starting therapy (designated phase I), addition of firstly a bDMARD [an anti-TNF agent (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved biosimilar DMARDs), abatacept, IL-6 inhibitors, or rituximab] or secondly a Jak inhibitor should be considered either following an alternative synthetic DMARD strategy or in place of an alternative synthetic DMARD strategy (designated phase II) (Fig. 2) [6]. In the scenario where this first trial of biologic therapy fails, an alternative bDMARD should be considered (an alternative anti-TNF agent, abatacept, IL-6 inhibitor, or rituximab) or a Jak inhibitor. However, it would be expected that, even when current treatment algorithms for rheumatic disease are followed, a significant proportion of patients treated with bDMARDs would be unresponsive to treatment, would lose responsiveness [10] or would experience unacceptable side effects leading to withdrawal [11].

Considerable debate has existed over whether originator and biosimilar medicines can be considered interchangeable and whether switching or substitution of biologic medicines is appropriate. Furthermore, the use of different terms, such as interchangeability, switching and substitution, has also been a source of some confusion [58] (Table 2). European guidelines consider biosimilar anti-TNF agents to be interchangeable with their reference anti-TNF products, although they should not be considered as a replacement [6] in the case of failed efficacy or unacceptable toxicity. Given the view that biosimilars are interchangeable with their reference products, when should they be used? One might consider that they may be used as any part of the treatment algorithm for certain conditions. However, this in itself brings uncertainty as to whether physicians would adopt such an approach. Certainly, biologic-naïve patients are clear candidates for use of biosimilars. Moreover, patients who are already on a reference biologic can be considered for transition to a biosimilar after appropriate discussion with a specialist. To date, experience from clinical trials, real-world studies and post-marketing experience has provided reassuring data regarding the efficacy and safety of switching patients with a range of rheumatic and inflammatory diseases from reference infliximab to the biosimilar, CT-P13 [59]. In particular, blinded studies have demonstrated that switching from reference infliximab to CT-P13 does not result in any loss of efficacy, increase in AEs or increase in immunogenicity [23, 24]. Although open-label switching can be undertaken in clinical practice, recent discontinuation rates reported in clinical trials for patients switching from reference infliximab to CT-P13 have been attributed to subjective reasons (negative expectations) and a possible nocebo effect [28, 29, 60]. Promising results have also been reported in patients switching from reference infliximab to the biosimilar SB2 and in patients switching from reference etanercept to the biosimilar SB4 [37, 46]. However, the question of switching from a reference product during successful therapy remains undetermined.

The use of biosimilars in rheumatology has been a hot topic in recent years, with some physicians being cautious about using them in clinical practice [61]. This at least, in part, appears to reflect potential uncertainties among

FIG. 2 Algorithm based on the 2016 EULAR recommendations on RA management



[a]2010 ACR-EULAR classification criteria can support early diagnosis. [b]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [c]MTX should be part of the first treatment strategy; while combination therapy of csDMARDs is not preferred by the Task Force, starting with MTX does not exclude its use in combination with other csDMARDs. [d]TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6 inhibitors or rituximab; in patients who cannot use csDMARDs as co-medication, IL-6 inhibitors and tsDMARDs have some advantages. [e]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak inhibitors). [f]The most frequently used combination comprises MTX, SSZ and HCQ. [g]Dose reduction or interval increase can be safely done with all bDMARDs with little risk

Table 2 Definitions of interchangeability, substitution and switching

Interchangeability	The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber
Substitution	Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber
Switching	Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment

Information taken from [58].

some prescribers regarding the utility of biosimilars [59]. Confidence in the clinical profile of these agents should arise from an understanding of the extensive and rigorous process undertaken to establish comparability between the biosimilar and the reference medicinal product [12]. Generally, biologic agents are associated with a high cost, which not only tests the budgets of patients and payers, but also has a detrimental effect on access to these agents, reflecting budget restrictions in many countries [62]. This has resulted in wide inequalities in their use [9]. Given that biosimilars are generally a lower cost alternative to reference medicinal products [9], this may well have an effect on uptake and prescribing behaviour. A greater number of eligible patients might be treated and inequalities in healthcare provision may begin to dissipate [9]. Indeed, budget impact analyses of the introduction of a biosimilar in several European countries have shown that switching to biosimilar therapy could result in significant cost savings and increase access to effective biologic therapy [63–65]. Significant cost savings can be made both by switching patients to a biosimilar from a reference medicinal product and offering biosimilars to patients that are treatment naïve. However, further evidence from pragmatic clinical trials that compare the most effective conventional treatment strategies with the use of biosimilars for inducing remission are required before initiation of biosimilars in treatment-naïve patients can be recommended, irrespective of the potential reduced costs.

Lower cost and increased access might also translate into greater use of biosimilars in the first-line biologic setting for certain conditions. A similar scenario could be imagined in the second and subsequent phases of biologic use. Initiating a biosimilar in treatment-naïve patients, or switching a patient to a biosimilar due to lack of efficacy or tolerability to a different reference biologic agent, is likely, however, to be considered in a different light to switching *during* successful treatment solely on the basis of cost. There are no specific guidelines on switching to a biosimilar and so this approach will come down to physician–patient judgement and should involve an informed decision-making process. Likewise, there is little evidence available to guide switching to a biosimilar in clinical practice, although real-world data, including the NOR-SWITCH study, are being collected. As such, it is crucial that high-quality pharmacovigilance and registry data are collected when transitioning patients to a biosimilar.

Automatic switching is one area that might cause particular concern, as this would not involve physician consultation and may impact effective pharmacovigilance, which is dependent on the transparent use of nomenclature and treatment history. In Europe, the EMA does not have the authority to designate a biosimilar to be an automatic substitute at the pharmacy [66], but such an approach could be accommodated within individual nations [52]. Notably, in Australia, the body involved with listing medicines for reimbursement—the Pharmaceutical Benefits Advisory Committee—has taken the decision to award a flag to the infliximab biosimilar Inflecta™. The awarding of this flag means that Inflecta™ and the innovator Remicade® are now substitutable at the pharmacy level once the pharmacist has consulted with the patient [67].

Essentially, as more data become available, they need to be carefully scrutinized in order for an informed decision to be made as to the potential place of biosimilars in clinical practice.

Discussion

As of March 2017, three anti-TNF biosimilar agents have been granted approval and are available on the market for patients with rheumatic diseases in the EU. The infliximab (Remicade®) biosimilars CT-P13 (Remsima® and Inflectra®) and SB2 (Flixabi®) and the etanercept

Fig. 2 Continued
of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon reinstitution of the same bDMARD. [h]Efficacy and safety of bDMARDs after Jak inhibitor failure is unknown; also, efficacy and safety of an IL6-pathway inhibitor after another one has failed is currently unknown. [i]Efficacy and safety of a Jak inhibitor after insufficient response to a previous Jak inhibitor is unknown. bDMARD: biologic DMARD; bsDMARD: biosimilar DMARD; csDMARD: conventional synthetic DMARD; EMA: European Medicines Agency; FDA, Food and Drug Administration; tsDMARD: targeted synthetic DMARD. Reproduced from EULAR recommendations for the management of RA with synthetic and biologic DMARDs: 2016 update, Smolen *et al*. ©2017 [6], with permission from BMJ Publishing Group Ltd.

(Enbrel®) biosimilar SB4 (Benepali®) have shown close comparability to their reference medicinal products in terms of their physical, biologic and clinical characteristics, having undergone extensive evaluations. International guidelines on the treatment of RA, in particular, have acknowledged the role of biosimilars in terms of their interchangeability with reference bDMARDs, except in the case of lack of efficacy or tolerability. A similar approach can expect to be adopted in other rheumatic diseases. Given that cost is a barrier to effective bDMARD use, the introduction of less costly biosimilars is likely to widen access and dissipate treatment inequalities in several markets. Physicians faced with prescribing decisions should be reassured by the robust and exhaustive EMA process that is involved in determining the comparability of biosimilars with their reference medicinal products. *De novo* usage of a biosimilar and switching to a biosimilar following lack of efficacy of or lack of tolerability to a different reference biologic agent are likely to be strategies that are most easily adopted. Switching during successful treatment at the physician's discretion should not be discounted given the potential cost implications, but more clinical experience is needed to ease current concerns. Overall, the introduction of biosimilar agents has the potential to widen patient access to effective biologic therapy, to better accommodate restraints within healthcare budgets and to improve overall patient outcomes.

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