Effectiveness of biosimilar infliximab CT-P13 compared to originator infliximab in biological-naive patients with rheumatoid arthritis and axial spondyloarthritis: data from the Portuguese Register Reuma.pt

Marona, J.; Sepriano, A.; Ramiro, S.; Almeida, D.; Brites, L.; Couto, M.; ... ; Araújo, F.C.

ARP Rheumatology 2023;2:132-140

ORIGINAL ARTICLES

Effectiveness of biosimilar infliximab CT-P13 compared to originator infliximab in biological-naïve patients with rheumatoid arthritis and axial spondyloarthritis: data from the Portuguese Register Reuma.pt

Marona J[1], Sepriano A[2], Ramiro S[3], Almeida D[4], Brites L[5], Couto M[6], Cunha I[7], Fernandes BM[8], Garcia J[9], Melo AT[10], Nóvoa T[11], Oliveira M[12], Pinto P[13], Santos MJ[14], Silva C[15], Fonseca JE[10], Araújo FC[16]

ABSTRACT

Objectives: To compare the effectiveness of the infliximab biosimilar (sim-INF) CT-P13 with originator infliximab (orig-INF) over 24 months of follow-up in biological-naïve patients with rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA).

Methods: Biological-naïve patients from the Rheumatic Diseases Portuguese Register (Reuma.pt), with a clinical diagnosis of RA or axSpA, who were starting either the sim-INF CT-P13 or the orig-INF after 2014 (date of market entry of CT-P13 in Portugal), were included. Patients on biosimilar and originator were compared regarding different response outcomes at 3 and 6 months, adjusting for age, sex and baseline C Reactive Protein (CRP). The main outcome was the change in DAS28-Erythrocyte Sedimentation Rate (ESR) for RA and the ASDAS-CRP for axSpA. Additionally, the effect of sim-INF vs orig-INF on different response outcomes over 24 months of follow-up was tested with longitudinal generalized estimating equations (GEE) models.

Results: In total, 140 patients were included, 66 (47%) of which with RA. The distribution of patients starting the sim-INF and the orig-INF was the same between the two diseases (approximately 60% and 40%, respectively). From the 66 patients with RA, 82% were females, mean age was 56 (SD 11) years and mean DAS28-ESR 4.9 (1.3) at baseline. As for the patients with axSpA, 53% were males, mean age was 46 (13.0) years and mean ASDAS-CRP 3.7 (0.9) at baseline. There were no differences in efficacy between RA patients treated with the sim-INF and the orig-INF, either at 3 months (ΔDAS28-ESR: -0.6 (95% CI -1.3; 0.1) vs -1.2 (-2.0; -0.4)), or at 6 months (ΔDAS28-ESR: -0.7 (-1.5; 0.0) vs -1.5 (-2.4; -0.7)). This was also true for patients with axSpA (ΔASDAS at 3 months: -1.6 (-2.0; -1.1) vs -1.4 (-1.8; -0.9) and at 6 months: -1.5 (-2.0; -1.1) vs -1.1 (-1.5; -0.7)). Results were similar with the longitudinal models over 24 months.

Conclusion: There are no differences in effectiveness between the sim-INF CT-P13 and the orig-INF in the treatment of biological-naïve patients with active RA and axSpA in clinical practice.

Keywords: Spondylarthritis; Rheumatoid arthritis; Biosimilar; infliximab; CT-P13; Axial spondyloarthritis.

INTRODUCTION

Biological disease-modifying antirheumatic drugs (bDMARDs) are a pillar of the treatment of rheumatic diseases such as Rheumatoid Arthritis (RA) and axial Spondyloarthritis (axSpA)[1-3]. These drugs are also the current main drivers of direct costs of healthcare systems worldwide which might, partially, explain why they are yet to become equally accessible to all rheumatic patients[4,5]. The end of patents for some bDMARDs allowed manufacturers to develop biosimilar drugs, which contain a version of the active substance of their originators. Even

[1] Rheumatology, Centro Hospitalar e Universitário Cova da Beira ORCID: 0000-0003-1595-6497; [2] Rheumatology, Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental; [3] Rheumatology, Leiden University Medical Center; [4] Rheumatology, Unidade Local de Saúde do Alto Minho; [5] Rheumatology, Centro Hospitalar de Leiria; [6] Rheumatology, Centro Hospitalar Tondela-Viseu; [7] Rheumatology, Centro Hospitalar do Baixo Vouga; [8] Rheumatology, Centro Hospitalar de São João; [9] Rheumatology, Centro Hospitalar do Médio Tejo; [10] Rheumatology and Metabolic Bone Diseases Department, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte; [11] Rheumatology, Hospital Divino Espírito Santo; [12] Rheumatology, Centro Hospitalar e Universitário Cova da Beira; [13] Rheumatology, Centro Hospitalar de Vila Nova de Gaia e Espinho; [14] Rheumatology, Hospital Garcia de Orta; [15] Rheumatology, Instituto Português de Reumatologia; [16] Rheumatology and Osteoporosis Unit, Hospital Ortopédico de Sant'Ana

Submitted: 20/07/2022
Accepted: 16/04/2023

Correspondence to: José Marona
E-mail: jaom495@hotmail.com

though biosimilars are made using independently-derived cell lines and separately-developed manufacturing processes, they intend to be as effective and safe as their originators but, importantly, less expensive[6,7].

Infliximab's biosimilar (sim-INF) CT-P13 was the first monoclonal antibody (mAb) to be approved by the European Medicines Agency (EMA) in 2013[8]. The clinical efficacy of CT-P13 was established in two 30-week randomized clinical trials (RCTs): the phase I PLANETAS in patients with radiographic axSpA and the phase III PLANETRA in patients with RA[9,10]. These studies demonstrated similar efficacy and safety profiles between CT-P13 and its originator.

The approval of CT-P13 was shortly followed by the approval of other biosimilars with reassuring evidence on their efficacy and safety stemming not only from clinical trials but also from 'real-life' settings[7]. Most observational studies including patients with RA and SpA have assessed infliximab switch, sometimes disfavouring the biosimilar product[11-13]. This has largely been attributed to a nocebo effect[14], although the evidence for such an effect has been disputed[15]. In order to (also) address this issue, a large prospective study with data from five biologic national registers from Northern Europe included only biological-naïve patients with SpA who were starting either the infliximab originator (orig-INF) or the CT-P13 (sim-INF)[16]. After 2 years of treatment no differences were found in disease activity markers comparing both products. Still, real-world data continues to be gathered and, besides the latter, only a few studies have compared bDMARD-naive patients starting treatment with a bDMARD originator versus the biosimilar during the same time period in RA and axSpA.

We aimed at comparing the effectiveness of the sim-INF CT-P13 with orig-INF over 24 months of follow-up in biological-naïve patients with RA and axSpA followed in daily clinical practice.

METHODS

Patients and study design

This was a prospective multicentre cohort study in which adult patients (≥18 years old) diagnosed with RA or axSpA (according to their rheumatologists), registered in Reuma.pt (Rheumatic Diseases Portuguese Register) were included. Reuma.pt is a nationwide cohort, established and managed by the Portuguese Society of Rheumatology, in which data from patients with various rheumatic diseases, including RA and axSpA, is recorded[22]. Two groups were defined: 1) patients starting the sim-INF CT-P13; and 2) patients starting orig-INF. They were starting their first bDMARD either due to inefficacy, intolerance or adverse events to conventional therapies (i.e., conventional synthetic DMARDs (csDMARDs) and/or non-steroidal anti-inflammatory drugs (NSAIDs)), according to their treating rheumatologists. Follow-up started with the first drug administration since the market entry of CT-P13 in Portugal, that was January 2014 (baseline), and ended at treatment discontinuation or at the end of the study period (December 2019). Follow-up visits occurred after 3, 6, 12, 18 and 24 months. In addition to being naïve for bDMARD therapy, patients in both groups were also required to have baseline visit registration available.

In Portugal bDMARDs are fully reimbursed, which contributes to level the access to these expensive therapies. Despite the fact that, in the first months of the introduction of CT-P13 in the Portuguese market, the decision of initiating an originator or a biosimilar was somehow shared between rheumatologists and hospital pharmacies, the latter always favoured the standard use of the cheapest drug as the initial bDMARD treatment, especially in recent years (unless explicitly 'challenged' by the treating rheumatologists).

For this study, a dedicated team of researchers from each participating centre was assigned to complete missing information in Reuma.pt whenever possible. Reuma.pt has been approved by the ethics committees of the participating hospitals and this specific study has been approved by the ethics committee of the Nova Medical School, Lisbon, Portugal (nr.45/2016/CEFCM). Patients have signed a written informed consent before inclusion.

Demographic and clinical characteristics

Information on treatment was available in each visit. In this case we specifically focused on whether the patient was treated with sim-INF or orig-INF (including start and stop dates).

The following characteristics were collected at baseline: i. Socio-demographic: age, sex, body mass index (mg/m^2), smoking status (smoker vs non-smoker); ii. Clinical and laboratory: disease duration (years), C-reactive protein (CRP) (mg/dL), erythrocyte sedimentation rate (ESR), the number of comorbidities (arterial hypertension, dyslipidaemia, diabetes, cardiovascular diseases, thyroid disease and malignancies) and the past and current comedication (NSAIDs, oral glucocorticoids and csDMARDs).

Disease-specific data included: i. RA: serology: rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA); ii. axSpA: SpA features all defined as ever (i.e. current or past) and binary (yes/no): inflammatory back pain (no formal definition), peripheral arthritis, uveitis, inflammatory bowel disease (Crohn's/ulcerative colitis), psoriasis, dactylitis, heel enthesitis,

good response to NSAIDs, elevated CRP (≥0.5mg/dL), human leukocyte antigen B27 status (HLA-B27) and familial history of SpA[17]; Imaging: presence of definite radiographic sacroiliitis according to the modified New York criteria (mNY) (according to the treating rheumatologists/local radiologists)[18].

Treatment outcomes

Treatment outcomes were assessed with change and status scores. Change-scores were assessed as the difference between the value in each follow-up visit and the value at baseline. Status scores were assessed in each follow-up visit.

In RA, treatment effect was assessed according to the change in the 28-joint disease activity score (DAS) 28 – ESR (DAS28-ESR) (main outcome), DAS28-ESR remission (DAS28-ESR < 2.6) and low disease activity (DAS28-ESR ≤ 3.2), change in the clinical disease activity index (CDAI), CDAI remission (CDAI ≤ 2.8) and low disease activity (CDAI ≤ 10), change in the simplified disease activity index (SDAI), SDAI remission (SDAI ≤ 3.3) and low disease activity (SDAI ≤ 11), proportion of patients achieving the ACR/EULAR Boolean-based definition of remission and change in HAQ-score[19,20].

In axSpA, the effect of treatment was assessed according to the change in the Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP) (main outcome), ASDAS inactive disease (ASDAS < 1.3) and low disease activity (ASDAS < 2.1), ASDAS clinically important (ASDAS CII) (ASDAS Δ ≥ 1.1) and major improvement (ASDAS MI) (ASDAS Δ ≥ 2.0), change in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), BASDAI 50 response (i.e. improvement of BASDASI of ≥ 50% and/or absolute improvement of 2 units) and the change in the bath ankylosing spondylitis functional index (BASFI)[21].

Statistical analysis

The effect of treatment with sim-INF vs orig-INF on the response outcomes was evaluated separately for RA and axSpA, using two analytical approaches: i) multivariable linear (or logistic, depending on the outcome) regression using as outcome each response criteria at 3 and 6 months and adjusting for age, sex and CRP at baseline (selected a priori on clinical grounds). This analysis was performed only in patients with complete 6 months of follow-up (baseline, 3 and 6 months visits available) and with complete data for each response outcome; ii) multivariable linear (or binomial, depending on the outcome) generalized estimating equations (GEE), with the effect of treatment at baseline tested against the outcome over 24 months of follow-up (3, 6, 12, 18 and 24 months visits), accounting for the correlation of repeated measurements within patient and also adjusting for the same confounders (with CRP modelled as time-varying). This analysis was performed in all included patients regardless of their follow-up time.

Data analysis was performed using Stata V. 14.0.

RESULTS

Patient characteristics

By the time of database lock, 154 biological-naïve patients registered in Reuma.pt who started therapy with infliximab (either the sim-INF CTP-13 or the orig-INF) fulfilled the inclusion criteria for this analysis. From these, 14 patients did not have registration of the baseline visit. In total, 140 patients were included (n=66, 47% with RA; n=74, 53% with axSpA). The proportion of patients starting the sim-INF and the orig-INF was the same between the two diseases (58% for the biosimilar [n=38 for RA and n=41 for axSpA] and 42% for the originator [n=28 for RA and n=31 for axSpA]).

Baseline characteristics are shown in table 1 and table 2, for RA and axSpA, respectively. From the 66 patients with RA, 82% (n=54) were females, had a mean age of 56 (SD 11) years and mean DAS28-ESR of 4.9 (1.3) at baseline. As for the axSpA patients, 53% (n=39) were male, had a mean age of 46 (13) years and a mean ASDAS-CRP of 3.7 (0.9) at baseline. There were some differences in baseline characteristics between the sim-INF CT-P13 and the orig-INF that should be pointed out: 1) a slightly higher disease activity in the sim-INF group for both patients with RA (DAS28-ESR: 5.1 (1.2) vs 4.8 (1.5), for sim-INF and orig-INF, respectively) and with axSpA (ASDAS-CRP: 3.8 (0.9) vs 3.5 (0.9), for sim-INF and orig-INF, respectively); 2) for patients with RA, a higher proportion of males and positive serology were present in the orig-INF group compared to sim-INF; 3) for patients with axSpA, a higher proportion of males, smokers, HLA-B27 positivity and radiographic sacroiliitis were present in the orig-INF group compared to sim-INF.

Treatment effect of sim-INF vs orig-INF at 3 and 6 months

In total, 85 patients (41 with RA and 44 with axSpA) had complete 6-month follow-up, once again with a similar distribution between sim-INF and orig-INF (46% and 43% for RA and axSpA, respectively, in the sim-INF group). The remaining 55 patients (from the original 140) were excluded mostly due to missing data (n=39; 71%). Reasons for discontinuation of therapy before 6 months regarding the residual 16 patients, are included in the supplementary Table I.

Table I. Baseline patient- and disease-characteristics of patients with rheumatoid arthritis

Variables	Overall (N=66)	Originator (N=28)	Biosimilar (N=38)
Age in years	56 (11)	55 (12)	56 (11)
Gender (male)	12 (18)	7 (25)	5 (13)
Current smokers †	11 (20)	5 (20)	6 (20)
Number of comorbidities * †	0.6 (0.7)	0.4 (0.6)	0.7 (0.8)
Disease duration in years †	9 (7)	10 (7)	9 (7)
RF †	51 (82)	23 (92)	28 (76)
ACPA †	45 (78)	19 (86)	26 (72)
DAS28-ESR (3V) †	4.9 (1.3)	4.8 (1.5)	5.1 (1.2)
CRP, mg/dL ‡	1.9 (2.3)	1.9 (2.0)	1.9 (2.6)
ESR, mm/h ‡	39.7 (28.8)	31.5 (21.4)	46.3 (32.4)
Co-medication †			
NSAIDs	28 (42)	15 (54)	13 (34)
csDMARDs	59 (94)	25 (93)	34 (94)
Oral Corticosteroids	48 (77)	19 (73)	29 (81)

Overall: RA patients from Reuma.pt, irrespective of treatment group. Continuous variables presented as mean ± SD; categorical variables presented as n (%). ‡ <5% of missing values. † <25% of missing values. * Arterial hypertension and other cardiovascular diseases, dyslipidemia, diabetes mellitus, thyroid disease and malignancies. bDMARDs, biologic Disease Modifying Anti-Rheumatic Drugs. RF, Rheumatoid Factor. ACPA, Anti-Citrullinated Peptide Antigen. DAS28 (3V), Disease Activity Score-28 (3 variables). CRP, C Reactive Protein. ESR, Erythrocyte Sedimentation Rate. NSAIDs, Non-Steroid Anti-inflammatory Drugs. csDMARDs, conventional synthetic Disease Modifying Anti-Rheumatic Drugs.

Overall, response to sim-INF and orig-INF was similar according to each outcome at 3 and 6 months, for both RA (e.g., Δ DAS28-ESR at 6 months β biosimilar vs originator= 0.8 (95% CI -0.4;1.9) (Table III) and for axSpA (e.g., Δ ASDAS-CRP at 6 months β biosimilar vs originator= -0.5 (95% CI -0.1;1.1) (Table IV). For a few outcomes in axSpA the likelihood of response was higher for sim-INF in comparison with the orig-INF (i.e., ASDAS CII at 3 months OR 6.7 (95% CI 1.1;39.5), ASDAS MI at 6 months OR 8.4 (95% CI 1.1;63.3); p-value 0.04 for both. However, the confidence interval in both cases was also very large.

Treatment effect of sim-INF vs orig-INF over 24 months

The effect of treatment at baseline on each response outcome over 24 months of follow-up is shown in Table V. There was again no difference in response between the two groups according to the different outcomes either for RA (e.g., DAS28-ESR over 24 months: β 0.6 (95% CI 0.2;1.1)) or for axSpA (e.g., ASDAS-CRP over 24 months: β 0.0 (95% CI -0.4;0.3)).

DISCUSSION

In this prospective cohort study, we found no significant differences in response outcomes over 24 months among biological-naïve patients who had started treatment with sim-INF CT-P13 or orig-INF, neither for RA nor axSpA. Thus, these results support the similarity of both treatments in respect to their effectiveness in daily clinical practice.

Following regulatory approval of sim-INF CT-P13 in Europe, the majority of post-marketing studies have assessed the effect of switching to a biosimilar among patients already under treatment with bDMARD originators. These include the long-term extensions of the original RCTs that led to CT-P13 approval for RA and axSpA (PLANETRA and PLANETAS), as well as the NOR-SWITCH study, all of which corroborating the equivalence of the efficacy of sim-INF CT-P13 and orig-INF[23-25].

The first 'real-world' evidence supporting the effectiveness of CT-P13 in RA and axSpA also derive from studies in which patients switched from orig-INF[11-13]. Of interest, a recent Portuguese study has showed that the switch in routine care of a group of RA, axSpA and psoriatic arthritis patients from orig-INF to sim-INF CT-P13 did not affect efficacy, safety, immunogenicity and reduced costs in 26.4%[26].

Only more recently, the effectiveness of sim-INF CT-P13 as first-line biologic therapy in RA and axSpA was also evaluated[16, 27-30]. These include studies comparing

Table II. Baseline patient- and disease-characteristics of patients with axial spondyloarthritis

Variables	Overall (N=74)	Originator (N=31)	Biosimilar (N=43)
Age in years	46 (13)	48 (13)	45 (13)
Gender (male)	39 (53)	21 (68)	18 (42)
Current smokers †	19 (30)	12 (46)	7 (18)
Number of comorbidities * †	0.3 (0.5)	0.3 (0.4)	0.3 (0.6)
Disease duration in years †	14 (11)	15 (11)	12 (11)
Number of SpA features ** ‡	2.9 (1.3)	2.6 (1.4)	3.1 (1.2)
HLA-B27 †	41 (69)	18 (78)	23 (64)
mNY †	54 (82)	25 (89)	29 (76)
Inflammatory back pain, ‡	58 (84)	22 (82)	36 (86)
Peripheral arthritis, ‡	25 (36)	12 (44)	13 (31)
Anterior uveitis, ‡	9 (13)	3 (11)	6 (14)
Psoriasis, ‡	1 (1)	0 (0)	1 (2)
Inflammatory bowel disease, ‡	14 (20)	3 (11)	11 (26)
BASDAI (0-10) ‡	6.3 (2.1)	5.6 (2.4)	6.7 (1.8)
ASDAS-CRP ‡	3.7 (0.9)	3.5 (0.9)	3.8 (0.9)
BASFI (0-10) ‡	5.9 (2.4)	5.6 (2.4)	6.1 (2.3)
CRP, mg/dL ‡	1.7 (1.9)	1.7 (1.5)	1.7 (2.1)
ESR, mm/h ‡	34.9 (23.5)	31.0 (20.2)	37.2 (25.2)
Co-medication			
NSAIDs	33 (45)	14 (45)	19 (44)
csDMARDs	38 (51)	18 (58)	20 (47)
Oral Corticosteroids	12 (16)	6 (19)	46 (14)

Overall: axSpA patients from Reuma.pt, irrespective of treatment group. Continuous variables presented as mean ± SD; categorical variables presented as n (%). ‡ <10% of missing values. † <25% of missing values. * Arterial hypertension and other cardiovascular diseases, dyslipidemia, diabetes mellitus, thyroid disease and malignancies. ** SpA features: inflammatory back pain, sacroiliitis on imaging (pelvic radiography and/or MRI), HLA-B27, peripheral arthritis, uveitis, inflammatory bowel disease, psoriasis, dactylitis, enthesitis, good response to NSAIDs, elevated CRP (≥0.5mg/dL) and familial history of SpA. HLA-B27, Human Leucocyte Antigen B27. mNY, modified New York criteria for Ankylosing Spondylitis. CRP, C Reactive Protein. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. BASFI, Bath Ankylosing Spondylitis Functional Index. ESR, Erythrocyte Sedimentation Rate. NSAIDs, Non-Steroid Anti-inflammatory Drugs. csDMARDs, conventional synthetic Disease Modifying Anti-Rheumatic Drugs.

biological-naïve patients starting sim-INF CT-P13 or the orig-INF during the same time period. This is relevant to limit, among others, the nocebo effect which has been reported mainly in the context of switching from originators[14]. The first and larger of these studies included patients with axSpA from several Northern registers and found no significant differences in disease activity between the ones assigned to receive sim-INF CT-P13 and those assigned to receive the orig-INF (ASDAS-CRP at 6 months: 2.03 (1.18) vs 1.95 (1.15))[16]. Two other studies from the Korean College of Rheumatology Biologics (KOBIO) register[27, 28] also found similar effectiveness between sim-INF CT-P13 and orig-INF both in patients with RA (ACR20 response at 24 months: 82.1% vs 62.1%) and axSpA (ASDAS MI at 24 months: 59.9% vs 56.9%), even though the comparison was not restricted to patients starting these therapies as first-line biologics.

Taken all together, our results are in agreement with previous evidence from 'real world' settings which support that the sim-INF CTP-13 and orig-INF are equally effective.

Our study has some limitations. The main limitation pertains to the small number of patients who fulfilled the inclusion criteria and could therefore be included. This is, however, translating daily clinical practice where rheumatologists have other bDMARDs at their disposal, including those administered subcutaneously which are arguably preferable to many patients. The small sample size may also account for some differences in baseline characteristics. Of note, our longitudinal analysis making use of GEE models allowed us to

Table III. Effect of treatment on response outcomes at 3 and 6 months in patients with rheumatoid arthritis (multivariable models)

Outcomes	Biosimilar vs Originator (N=41; 22 vs 19)			
	3 months	p-value	6 months	p-value
Continuous, b (95% CI)				
Δ DAS28-ESR (3V) †	0.6 (-0.4; 1.7)	0.23	0.8 (-0.4; 1.9)	0.18
Δ CDAI	0.1 (-11.6; 11.9)	0.98	2.4 (-9.8; 14.7)	0.69
Δ SDAI †	-1.9 (-14.6; 10.9)	0.77	1.7 (-11.6; 15.1)	0.80
ACR-EULAR Remission †	*	*	*	*
Dichotomous, OR (95% CI)				
DAS28-ESR (3V) <2.6 †	0.4 (0.0; 4.9)	0.47	0.6 (0.1; 3.1)	0.50
DAS28-ESR (3V) ≤3.2 †	0.3 (0.1; 2.3)	0.26	0.7 (0.2; 3.2)	0.70
CDAI≤2.8 †	0.8 (0.0; 15.8)	0.88	*	*
CDAI≤10 †	1.3 (0.2; 7.0)	0.74	1.2 (0.3; 5.5)	0.81
SDAI≤3.3 †	*	*	*	*
SDAI≤11 †	1.1 (0.2; 24.7)	0.90	1.8 (0.4; 8.9)	0.49

Comparison of the different response outcomes between patients treated with the infliximab biosimilar and those treated with the infliximab originator (multivariable logistic/linear regression using the originator as reference category and adjusted for age, sex and baseline CRP). b, Beta coefficient. OR, Odds Ratio. 95% CI, 95%. Continuous variables presented as b (95% CI); categorical variables presented as OR (95% CI). † <35% of missing values. DAS28 (3V), Disease Activity Score-28 (3 variables). DAS28 (3V) ESR<2.6, DAS28 Remission. DAS28≤3.2, DAS28 Low Disease Activity. CDAI, Clinical Disease Activity Index. CDAI≤2.8, CDAI Remission. CDAI≤10, CDAI Low Disease Activity. SDAI, Simple Disease Activity Index. SDAI≤3.3, SDAI Remission. SDAI≤11, SDAI Low Disease Activity. HAQ, Health Assessment Questionnaire. ACR-EULAR RC, American College of Rheumatology-European League Against Rheumatism Boolean Remission Criteria. Δ, difference between the corresponding outcome measure at the referred time-point and at baseline. * Models do not converge due to limited number of patients/events.

Table IV. Effect of treatment on response outcomes at 3 and 6 months in patients with axial spondyloarthritis (multivariable models)

Outcomes	Biosimilar vs Originator (N=44; 19 vs 25)			
	3 months	p-value	6 months	p-value
Continuous, β (95% CI)				
Δ ASDAS †	-0.2 (-0.8; 0.4)	0.52	-0.5 (-0.1; 1.1)	0.14
Δ BASDAI †	-0.4 (-1.9; 1.0)	0.55	-0.6 (-2.2; 0.9)	0.41
Δ BASFI †	-1.2 (-2.5; 0.2)	0.08	-0.9 (-2.2; 0.4)	0.18
Dichotomous, OR (95% CI)				
ASDAS CII †	6.7 (1.1; 39.5)	0.04	2.7 (0.5; 13.9)	0.24
ASDAS MI †	1.0 (0.2; 5.2)	0.99	8.4 (1.1; 63.3)	0.04
ASDAS LDA †	0.3 (0.0; 1.8)	0.17	1.2 (0.2; 6.4)	0.84
ASDAS ID †	0.6 (0.1; 3.1)	0.52	0.6 (0.1; 3.0)	0.49
BASDAI50 †	1.0 (0.2; 4.3)	0.98	1.6 (0.4; 7.0)	0.51

Comparison of the different response outcomes between patients treated with the infliximab biosimilar and those treated with the infliximab originator (multivariable logistic/linear regression using the originator as reference category and adjusted for age, sex and baseline CRP). β, Beta coefficient. OR, Odds Ratio. 95% CI, 95%. Continuous variables presented as b (95% CI); categorical variables presented as OR (95% CI). † <25% of missing values. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. BASFI, Bath Ankylosing Spondylitis Functional Index. BASFI, Bath Ankylosing Spondylitis Functional Index. BASDAI50, BASDAI 50 Response. ASDAS CII, ASDAS Clinical Important improvement. ASDAS MI, ASDAS Major Improvement. ASDAS LDA, ASDAS Low Disease Activity. Δ, difference between the corresponding outcome measure at the referred time-point and at baseline.

Table V. Effect of treatment on response outcomes over 24 months in patients with rheumatoid arthritis and axial spondyloarthritis (multivariable models)

Variables	Biosimilar vs Originator Rheumatoid Arthritis
Outcomes	
DAS28-ESR (3V) [N=65, n=200 visits]	0.6 (0.2; 1.1)
DAS28-ESR (3V) <2.6 [N=65, n=200 visits]	0.4 (0.1; 1.4)
DAS28-ESR (3V) ≤3.2 [N=65, n=200 visits]	0.5 (0.2; 1.2)
CDAI [N=56, n=172 visits]	2.3 (-1.5; 6.2)
CDAI≤2.8 [N=50, n=119 visits]	1.0 (0.9; 1.2)
CDAI≤10 [N=50, n=119 visits]	1.0 (0.8; 1.3)
SDAI [N=54, n=167 visits]	2.8 (-1.3; 7.0)
SDAI≤3.3 [N=49, n=115 visits]	1.1 (0.3; 4.0)
SDAI≤11 [N=49, n=115 visits]	1.2 (0.5; 3.0)
HAQ [N=54, n=126 visits]	0.4 (0.1; 0.7)
ACR-EULAR Remission [N=57, n=140 visits]	1.4 (0.4; 5.5)
	Axial Spondyloarthritis
Outcomes	
ASDAS [N=72, n=281 visits]	0.0 (-0.4; 0.3)
ASDAS CII [N=65, n=207 visits]	1.5 (0.6; 3.7)
ASDAS MI [N=65, n=207 visits]	2.8 (1.0; 8.2)
ASDAS LDA [N=68, n=212 visits]	0.7 (0.2; 2.1)
ASDAS ID [N=140, n=57 visits]	1.0 (0.5; 2.2)
BASDAI [N=73, n=284 visits]	0.1 (-0.7; 0.9)
BASDAI50 [N=67, n=210 visits]	1.1 (0.5; 2.5)
BASFI [N=68, n=265 visits]	-0.3 (-1.3; 0.7)

Generalized Estimating Equations (GEE) models with the treatment group as predictor (reference category: originator); all models adjusted for age, sex, and baseline CRP. b, Beta coefficient. OR, Odds Ratio. 95% CI, 95% Confidence Interval. Continuous variables presented as b (95% CI); categorical variables presented as OR (95% CI). DAS28, Disease Activity Score-28. DAS28 (3V) ESR<2.6, DAS28 Remission. DAS28≤3.2, DAS28 Low Disease Activity. CDAI, Clinical Disease Activity Index. CDAI≤2.8, CDAI Remission. CDAI≤10, CDAI Low Disease Activity. SDAI, Simple Disease Activity Index. SDAI≤3.3, SDAI Remission. SDAI≤11, SDAI Low Disease Activity. HAQ, Health Assessment Questionnaire. ACR-EULAR RC, American College of Rheumatology-European League Against Rheumatism Boolean Remission Criteria. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. BASFI, Bath Ankylosing Spondylitis Functional Index. BASFI, Bath Ankylosing Spondylitis Functional Index. BASDAI50, BASDAI 50 Response. ASDAS CII, ASDAS Clinical Important improvement. ASAS MI, ASDAS Major Improvement. ASDAS LDA, ASDAS Low Disease Activity..

include more patients, as compared to the completers' analysis, as well as to evaluate the efficacy outcomes at multiple visits per each patient, taking all the available information per patient into account. This setting allowed us to make a more efficient use of the available data and increased the statistical power to detect possible differences between groups therefore addressing, to some extent, the limitation of the sample size. Another limitation, common to all observational studies, is the possibility of confounding by indication. In fact, some differences were noted between patients starting sim-INF CT-P13 and the orig-INF, in particular in their levels of disease activity which were somewhat higher in the former group. There are several possible factors contributing to these differences: including local policies concerning the switch from originator to biosimilar, the beliefs of the prescribing rheumatologist which might have changed over time as more evidence accumulated supporting the use of biosimilars, and patients' preferences. The 'net result' of these sources of (selection) bias is difficult to quantify, therefore our results should be interpreted with caution. With that being said, it is still notable that no difference in efficacy was identified for almost all outcomes over a period up to 2 years of follow-up.

In summary, data from this nationwide multicentre cohort study has shown no differences in long-term effectiveness between the sim-INF CT-P13 and the orig-INF in the treatment of patients with active RA and ax-SpA, confirming that both drugs are a valid treatment option for these inflammatory diseases.

REFERENCES

1. Smolen JS, Landewé R, Bijlsma J, et al. 2016 Update of EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease odifying antirheumatic drugs. Ann Rheum Dis Published Online First: 06 March 2017. doi:10.1136/annrheumdis-2016-210715.
2. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis Published Online First: 13 January 2017. doi:10.1136/annrheumdis-2016-210770.
3. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis Published Online First: 07 December 2015. doi: 10.1136/annrheumdis-2015-208337.
4. Huscher D, Mittendorf T, von Hinüber U, et al. Evolution of cost structures in rheumatoid arthritis over the past decade. Ann Rheum Dis 2015;74:738–45.
5. Putrik P, Ramiro S, Kvien TK, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis 2014;73:198–206.
6. Araújo FC, Cordeiro I, Teixeira F, Gonçalves J, Fonseca JE. Pharmacology of biosimilar candidate drugs in rheumatology: a literature review. [Internet]. [cited 2019 Jun 4]. Available from:https://www.ncbi.nlm.nih.gov/pubmed/24811458.
7. Araújo FC, Gonçalves J, Fonseca JE, Biosimilars in Rheuma-

tology, Pharmacological Research (2019), doi: https://doi.org/10.1016/j.phrs.2019.104467.
8. European Medicines Agency. Remsima assessment report. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf. Accessed 23rd October 2018.
9. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallelgroup, prospective study comparing the pharmacokinetics, safety, and efficacy of CTP13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605–12.
10. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72:1613–20.
11. Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther 2015;15:1677-83
12. Benucci M, Gobbi FL, Bandinelli F, et al. Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study. Immunol Res 2017;65:419-22
13. Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017;76:1426-31
14. Tweehuysen L, van den Bemt BJF, van Ingen IL, et al. Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition From Reference Infliximab to Biosimilar Infliximab. Arthritis Rheumatol. 2018;70:60-68
15. Odinet JS, Day CE, Cruz JL, et al. The Biosimilar nocebo effect? A systematic review of double-blinded versus open-label studies. J Manag Care Spec Pharm 2018;24:952–9.
16. Lindström U, Glintborg B, Di Giuseppe D, et al. Treatment retention of infliximab and etanercept originators versus their corresponding biosimilars: Nordic collaborative observational study of 2334 biologics naïve patients with spondyloarthritis. RMD Open. 2019;5:e001079
17. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68(6):777-83.
18. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27(4):361--8.
19. England BR, Tiong BK, Bergman MJ, et al. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). 2019;71(12):1540-1555. doi:10.1002/acr.24042
20. Zhang B, Combe B, Rincheval N, Felson DT. Validation of ACR/EULAR definition of remission in rheumatoid arthritis from RA practice: the ESPOIR cohort. Arthritis Res Ther. 2012;14(3):R156. Published 2012 Jun 29. doi:10.1186/ar3896
21. Landewe R, van Tubergen A. Clinical Tools to Assess and Monitor Spondyloarthritis. Curr Rheumatol Rep 2015;17(7):47.
22. Canhão H, Faustino A, Martins F, et al. Reuma.pt - the rheumatic diseases portuguese register. Acta Reumatol Port 2011;36(1):45-56.
23. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis 2017;76:346–54
24. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2017;76:355–63.
25. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017;389:2304–16.
26. Valido A, Silva-Dinis J, Saavedra MJ, et al. Efficacy, immunogenicity and cost analysis of a systematic switch from originator infliximab to biosimilar CT-P13 of all patients with inflammatory arthritis from a single center. Efficacy, immunogenicity and cost analysis of a systematic switch from originator infliximab to biosimilar CT-P13 of all patients with inflammatory arthritis from a single center. Acta Reumatol Port. 2019;44(4):303-311.
27. Kim HA, Lee E, Lee SK, et al. Retention Rate and Safety of Biosimilar CT-P13 in Rheumatoid Arthritis: Data from the Korean College of Rheumatology Biologics Registry. BioDrugs. 2020;34:89-98
28. Kim HA, Lee E, Lee SK, Park YB, Shin K. Retention Rate and Efficacy of the Biosimilar CT-P13 Versus Reference Infliximab in Patients with Ankylosing Spondylitis: A Propensity Score-Matched Analysis from the Korean College of Rheumatology Biologics Registry. BioDrugs. 2020;34(4):529-539. doi:10.1007/s40259-020-00432-z
29. Codreanu C, Sirova K, Jarosova K, et al. Assessment of effectiveness and safety of biosimilar infliximab (CT-P13) in a real-life setting for treatment of patients with active rheumatoid arthritis or ankylosing spondylitis. Curr Med Res Opin. 2018;34:1763-1769
30. Gron KL, Glintborg B, Norgaard M, et al. Comparative Effectiveness of Certolizumab Pegol, Abatacept, and Biosimilar Infliximab in Patients With Rheumatoid Arthritis Treated in Routine Care: Observational Data From the Danish DANBIO Registry Emulating a Randomized Trial. Arthritis Rheumatol. 2019;71:1997-2004

SUPPLEMENTARY DATA

Table I. Reasons for discontinuation of bDMARD before 6 months of therapy

	Rheumatoid arthritis		Axial spondyloarthritis		Total
	Biooriginator	Biosimilar	Biooriginator	Biosimilar	
Discontinuations	5	5	4	2	16
Adverse event	1	1	1	0	3
Death	0	1	0	0	1
Inefficacy	0	1	1	1	3
Switch *	1	1	0	1	3
Unknown	3	1	2	0	6

* Reasons unknown