

## Original article

# Comparison of treatment retention of originator vs biosimilar products in clinical rheumatology practice in Sweden

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## Abstract

**Objectives.** To compare treatment retention between biosimilars and their originator products among first starters (etanercept, infliximab, adalimumab and rituximab), as well as after non-medical switch.

**Methods.** Patients with rheumatic diseases starting, for the first time, an originator or biosimilar etanercept, infliximab, adalimumab or rituximab were identified in the national Swedish Rheumatology Quality Register. Moreover, patients switching from an originator to its biosimilar were identified and individually matched to patients continuing on the originator. One-year treatment retention was calculated and hazard ratios (HR) for discontinuation with 95% CIs were estimated, adjusting for comorbidities and socio-economic factors.

**Results.** In total, 21443 first treatment courses were identified. The proportion of patients still on the drug at 1 year and the HR for discontinuation revealed no differences across adalimumab (Humira, Imraldi, Amgevita and Hyrimoz) nor across rituximab products (Mabthera, Ritemvia/Truxima and Rixathon). The proportions on the drug at 1 year were similar for Benepali (77%) and Enbrel (75%) and the adjusted HR for Benepali compared with Enbrel was 0.91 (95% CI 0.83, 0.99). For infliximab, the proportion still on the drug at 1 year was 67% for Remicade and 66% for Remsima/Inflectra and the HR compared with Remicade was 1.16 (95% CI 1.02, 1.33). Among 2925 patients switching from an originator drug to one of its biosimilars, we noted no statistically significant or clinically relevant differences in drug survival compared with those who remained on originator therapy.

**Conclusion.** This large observational study supports the equivalence of biologic DMARD biosimilar products and originators when used in routine rheumatology care.

**Key words:** biosimilar, bDMARDs, rheumatic diseases, retention

## Rheumatology key messages

- For etanercept, adalimumab, rituximab and infliximab, 53–67% of new starts were on a biosimilar.
- No clinically relevant differences in treatment retention were observed for biosimilars vs originators.
- No placebo effect with respect to treatment retention following non-medical switch was found.

## Introduction

Biosimilar products of biologic DMARDs (bDMARDs) entered the Swedish market in 2015 (the first infliximab

biosimilar was CT-P13) [1, 2]. Since then, several biosimilars of etanercept, adalimumab and rituximab have been marketed, with regulatory approvals based on head-to-head trials comparing the biosimilars with the

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respective originator products in a limited number of indications and during a limited study period, typically ~6 months [3].

For the first biosimilars marketed, the regulatory approvals were based on studies comparing new starts of the biosimilars and the originators [2, 4]. Equivalence between CT-P13 and the infliximab originator after switching treatment from the originator (non-medical switch) was first demonstrated in the NOR-SWITCH trial [5]. For biosimilars marketed more recently, equivalence after non-medical switch has primarily been demonstrated in open-label extensions (OLEs) to the original randomized controlled trials (RCTs) [6–9]. In contrast to the RCTs and their respective OLEs, a number of observational studies have reported inferior retention rates following non-medical switch in real life [10–12]. In order to explain these conflicting findings, the introduction of the biosimilars was accompanied by a debate regarding the inherent potential for a nocebo effect that could bias observational studies [13].

Throughout this period there has been a considerable increase in the use of biosimilars in Sweden, gradually replacing the originator drugs [14]. Hence, with a large number of patients in Sweden having either started a biosimilar product as their first exposure to that drug or having performed a non-medical switch to a biosimilar, it is now possible to compare the treatment retention of the biosimilars with their originators, both for new starts and after switching, for several different biosimilars in the same setting. Further, with biosimilars being widely used in routine rheumatology care, and with an ever-increasing number of new biosimilars being marketed, there is a clear need for maintained pharmacovigilance in order to detect unexpected differences in performance.

The main aim of the current study was to compare treatment retention between biosimilars and their originator products among first starters of etanercept, infliximab, adalimumab and rituximab in Sweden when used for different indications in routine rheumatology care. As a secondary aim, we evaluated if switching within the same drug affects treatment retention, using continued treatment with the respective originators as a reference.

## Methods

### Study design

This is an observational cohort study based on data from the Swedish Rheumatology Quality Register (SRQ). The SRQ has collected national data on rheumatology patients since 1995, including data on disease characteristics, lifestyle factors and treatments. The coverage of TNF inhibitors in the SRQ has been estimated to be >90% for patients with RA and 86% for SpA [15]. Data from the SRQ have been linked, using each patient's unique personal identification number, to other national Swedish registers (here, the National Patient Register and the Prescribed Drug Register) to obtain information on comorbidities and prescribed drugs and to the

Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) [16] to retrieve data on length of formal education (as a marker of socio-economic status).

In Sweden, the individual counties/regions are responsible for the tax-funded healthcare system. The counties/regions have separate tender processes for intravenous drugs (e.g. infliximab and rituximab), which may result in different pricing of these products and hence also differences in recommendations regarding choice of drug. In contrast, for the subcutaneous biosimilars/originators in this study, the pricing has been set through national contracts between authorities and pharmaceutical companies, resulting in substantial discounts. These contracts, and the resulting discounts, have changed markedly over time, influencing both the choice of biosimilar vs originator and the choice of drug.

### Study population

Patients in the SRQ starting a bDMARD for which there was at least one marketed biosimilar were identified from 1 March 2012 until the end date of the study period (31 December 2020). The identified bDMARDs were etanercept [originator: Enbrel; biosimilars: Benepali (SB4), Erelzi (GP2015)], infliximab [originator: Remicade; biosimilars: Remsima/Inflectra (CT-P13), Flixabi (SB2), Zessly (PF-06438179/GP1111)], adalimumab [originator: Humira; biosimilars: Imraldi (SB5), Amgevita (ABP501), Hyrimoz (GP-2017), Idacio (MSB11022)] or rituximab [originator: Mabthera; biosimilar: Ritemvia (CT-P10, later marketed as Truxima), Rixathon (GP2013)].

No restrictions based on indication were applied. Patients were classified as having RA [International Classification of Diseases (ICD) codes M05, M06, M12.5], PsA (ICD code M07.0, M07.2, M07.3, L40.5), AS (ICD code M45.9), SpA (ICD codes: M46.8, M46.9) or any other rheumatic condition (constituting 14% of infliximab use, 11% of etanercept, 13% of adalimumab and 8% of rituximab); see [Supplementary Table S1](#) (available at *Rheumatology* online) for the list of included rheumatic conditions in the 'other' category.

### Treatment retention among first-ever users of biosimilars vs originator products

For the main aim of comparing treatment retention of each biosimilar with their respective originator, only first-time starters of each drug were selected, irrespective of the line of treatment. Thus a patient who started Remicade during the study period as a first-ever infliximab (irrespective of any previous bDMARD treatment) but who later started Inflectra could contribute data to Remicade treatment but not to Inflectra. However, patients could contribute several treatment courses with different types of drugs. For each included treatment course, the crude treatment retention was determined, then visualized using Kaplan–Meier curves, capping the follow-up for infliximab at 60 months, etanercept at 48 months and adalimumab and rituximab at 24 months

(considering the time since market introduction of the first biosimilar of each drug). In addition, age- and sex-adjusted and fully adjusted (see Statistical analyses section) hazard ratios (HRs) for discontinuation were determined for each biosimilar using its respective originator as a reference.

Different follow-up periods were utilized, depending on the drug analysed, with the general rule (in order to maximize statistical precision) of including treatment starts (for the originator drug) up to 1 calendar year prior to the market introduction of its first biosimilar. Hence for infliximab, first-time treatment starts were included from March 2014, for etanercept from April 2015 and for adalimumab and rituximab from January 2018. Follow-up for all treatments ended at the date of discontinuation, censoring events, death or 31 December 2020, whichever occurred first. Discontinuation was defined as a lack of effectiveness or adverse events, according to the reason of discontinuation reported in the SRQ. Other reasons for interruption of the drug (including non-medical switch) were considered censoring events.

The PDR was used to identify and exclude patients who were prescribed any of the subcutaneous drugs according to the SRQ but who never dispensed the prescription at a pharmacy (4.4% for etanercept, 4.2% for adalimumab) and to identify patients where collected prescriptions of the studied originators/biosimilars did not align with the registered treatments in the SRQ.

#### Treatment retention following non-medical switch

For the secondary aim of comparing treatment retention after a non-medical switch, all patients who started (for the first time) an originator drug during the 3 years before the start of marketing of its first biosimilar were selected (here, initiators of etanercept originator from April 2013, initiators of originator infliximab from March 2012 and originators adalimumab and rituximab from January 2016). Using the prospectively recorded data in the SRQ, we identified those who had made a non-medical switch to a biosimilar product (defined as a discontinuation of the originator drug followed by a start of a biosimilar of the same molecule within 90 days). Each patient identified as having performed a non-medical switch was, at the time point of switching, matched to a patient who had received treatment with the originator drug for the same duration of time. The matching kept the calendar year of start of the originator, age and gender. The follow-up for drug retention/discontinuation started at the date of matching and ended at the date of discontinuation, censoring, death or 31 December 2020. Discontinuation and censoring were defined as in the main analyses.

As for the main analyses, the PDR was used to exclude patients who were not dispensed with the treatment reported in the SRQ (4.4% for etanercept, 4.1% for adalimumab).

#### Sensitivity analysis

Due to concerns that the coronavirus disease 2019 (COVID-19) pandemic may have impacted the results, a sensitivity analysis was performed for the primary aim with a reduced follow-up until 28 February 2020.

#### Covariates

Covariates included in the adjusted analyses were determined *a priori*, based on potential clinical relevance. Through the SRQ we retrieved information on the following disease characteristics at baseline, defined as the rheumatology visit closest to the recorded start of the treatment, within  $-90$  to  $+30$  days: disease duration, ESR and CRP levels, visual analogue scale for pain, disease activity levels (using 28-joint DAS with CRP for RA and PsA, and BASDAI for AS and SpA) and the concomitant use of conventional synthetic DMARDs (csDMARDs). Through the patient register we identified those patients registered with an ICD code for each of the following comorbidities in the 5 years prior to the start of the treatment: malignancy, diabetes, heart failure, myocardial infarction, chronic obstructive or interstitial pulmonary disease, kidney disease and infection. Additionally, inflammatory bowel disease, psoriasis and uveitis were identified for the SpA/AS patients (see [Supplementary Table S2](#) for ICD codes, available at *Rheumatology* online). We also adjusted for length of formal education, as a marker of socio-economic status.

#### Statistical analyses

Descriptive characteristics were tabulated using percentages, means and s.e.s. Retention rates were investigated by Kaplan–Meier estimation. HRs of discontinuation and their 95% CIs were estimated using Cox proportional hazards regression models, with each molecule analysed separately and the originator as a reference. The initial models were adjusted for age (categorical  $<40$ ,  $40- <50$ ,  $50- <60$ ,  $60- <70$ ,  $\geq 70$  years) and sex, while the fully adjusted models were additionally adjusted for indication (RA, PsA, SpA, AS, other), line of treatment (1, 2,  $\geq 3$ ), disease duration (continuous), length of formal education ( $\leq 9$  years, 10–12 years,  $>12$  years), calendar year of start of treatment (with the first 2 years collapsed together), geographical region (five regions in Sweden), concomitant use of csDMARDs (yes/no) and a comorbidity score (0, 1, 2 or  $\geq 3$  comorbidities among malignancy, diabetes, heart failure, myocardial infarction, chronic obstructive and interstitial pulmonary disease, chronic kidney disease and infection diagnosed 5 years prior to the start of the treatment).

It was prespecified that data for biosimilars with  $<50$  total exposed patients were not going to be presented and HRs for exposures with  $<10$  events (discontinuations) were not going to be estimated.

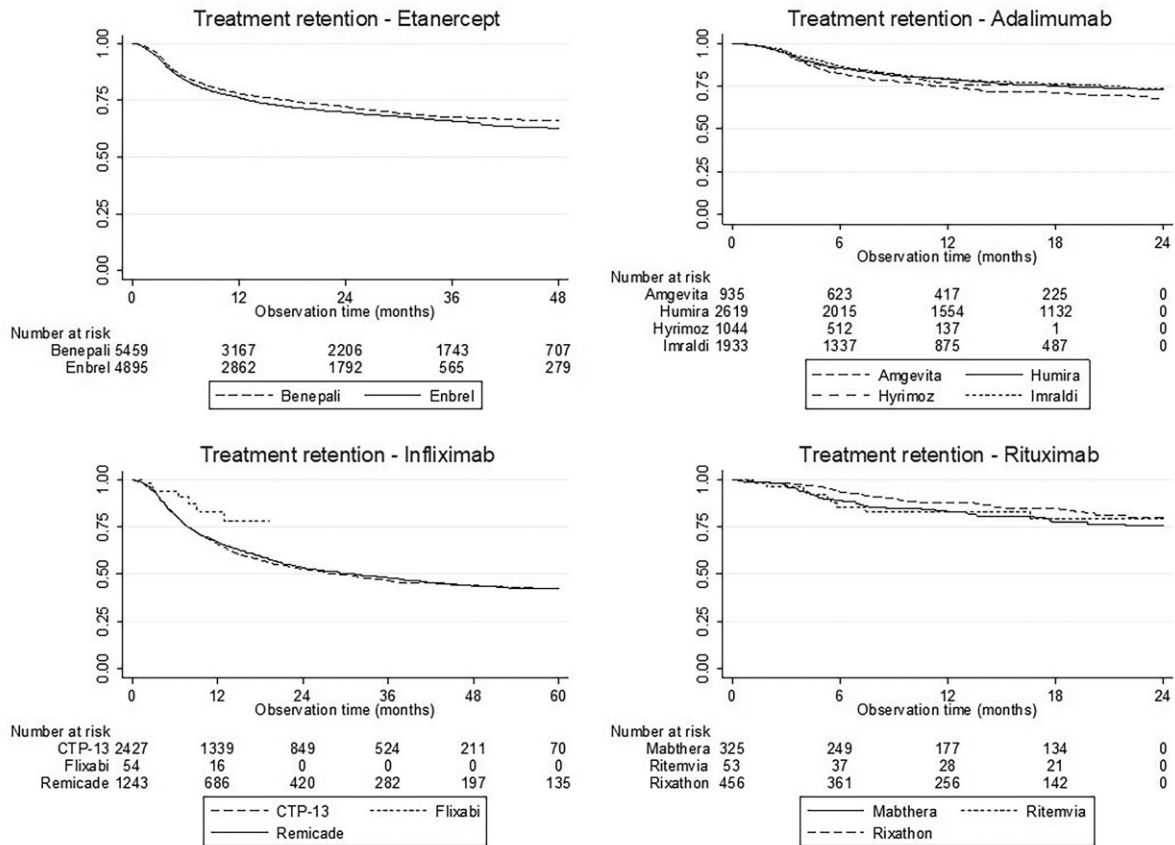
In addition, HRs stratified (instead of adjusted) by indication were estimated, further adjusted for disease activity (DAS28-CRP  $\leq 3.2$ ,  $3.2-5.1$  or  $\geq 5.1$  for RA and PsA; BASDAI  $<4$  or  $\geq 4$  for AS and SpA, plus a missing-

**TABLE 1** Baseline characteristics of patients starting etanercept, infliximab, adalimumab or rituximab for the first time

Characteristics	Etanercept		Adalimumab				Infliximab			Rituximab		
	Enbrel	Benepali	Humira	Imraldi	Amgevita	Hyrimoz	Remicade	Flixabi	CT-P13	Mabthera	Rixathon	Ritemvia
Patients, <i>n</i>	4895	5459	2619	1933	935	1044	1243	54	2427	325	456	53
Age, years, mean (s.d.)	51 (16)	51 (15)	47 (16)	50 (16)	51 (15)	51 (15)	49 (16)	50 (14)	49 (16)	62 (13)	62 (14)	60 (16)
Female, %	66	66	61	61	64	63	60	74	63	74	77	70
Indication, %												
RA	46	48	31	37	41	41	41	33	36	92	88	91
PsA	23	22	27	23	21	23	18	28	21	1	1	2
SpA	11	12	16	14	14	16	13	9	15	0	<1	0
AS	8	8	13	12	11	9	16	13	14	<1	<1	2
Other	12	10	14	14	13	11	13	17	14	6	10	6
Education (years), %												
≤9	16	15	13	14	15	15	22	11	20	22	21	23
10–12	48	49	46	49	53	50	49	50	48	45	49	43
>12	35	35	41	35	32	33	28	33	30	30	29	30
Missing	1	1	1	1	1	1	1	6	1	2	1	4
Disease duration, years, mean (s.d.)	11.1 (11.7)	11.1 (11.1)	11.7 (10.8)	11.7 (11.1)	12.6 (13.0)	10.5 (11.2)	10.9 (10.6)	10.1 (10.4)	11.2 (11.0)	15.6 (13.5)	14.1 (11.0)	16.9 (16.8)
ESR, mm/h, mean (s.d.)	20 (18)	21 (19)	18 (18)	21 (19)	21 (19)	20 (19)	23 (22)	28 (23)	22 (19)	32 (24)	30 (24)	30 (24)
CRP, mean (s.d.)	11 (18)	12 (18)	9 (17)	12 (19)	10 (17)	12 (20)	17 (26)	14 (17)	13 (22)	15 (22)	15 (19)	14 (13)
DAS28-CRP <sup>a</sup>	4.0 (1.2)	4.1 (1.2)	3.8 (1.2)	3.9 (1.1)	4.1 (1.2)	3.9 (1.2)	4.4 (1.2)	4.7 (1.3)	4.2 (1.1)	4.2 (1.2)	4.3 (1.3)	4.3 (1.1)
BASDAI <sup>b</sup>	5.2 (2.1)	5.3 (2.0)	5.1 (2.2)	5.0 (2.1)	5.6 (2.2)	5.1 (2.2)	5.9 (2.2)	6.1 (1.8)	5.6 (2.0)	–	–	–
Concomitant treatments												
Methotrexate	49	49	36	46	46	42	59	56	51	47	48	49
Other csDMARDs	14	15	10	13	12	10	14	15	13	19	17	8
Comorbidity score <sup>c</sup> (last 5 years), %												
0	65	67	66	69	67	68	65	69	66	44	45	32
1	29	27	29	26	27	25	29	28	29	37	36	38
2	5	5	4	5	5	5	5	4	4	14	15	19
3	1	1	1	1	1	1	1	0	1	6	5	11
Comorbidities (last 5 years), %												
Malignancy	4	4	3	4	4	4	3	4	3	15	13	21
COPD	2	2	1	2	2	2	3	2	2	13	14	11
Heart failure	1	1	1	1	1	2	1	0	1	3	5	9
Diabetes	6	6	5	5	6	5	5	2	5	8	8	11
Myocardial infarction	2	1	1	1	2	1	1	0	1	3	2	8
Chronic kidney disease	1	1	1	1	1	1	1	0	2	2	2	4
Knee or hip prosthesis	0	0	0	0	0	0	0	0	0	0	0	0
Infection	27	25	28	23	24	25	29	28	27	38	36	47
IBD <sup>b</sup>	3	2	8	6	8	4	8	17	8	–	–	–
Psoriasis <sup>b</sup>	6	6	6	6	6	4	7	8	5	–	–	–
Uveitis <sup>b</sup>	10	10	22	19	22	22	16	58	19	–	–	–

<sup>a</sup>Only RA and PSA patients. <sup>b</sup>Only SpA and AS patients. <sup>c</sup>Comorbidity score is the sum of different comorbidities (malignancy, diabetes, heart failure, myocardial infarction, chronic obstructive and interstitial lung disease, kidney disease and infection diagnosed 5 years prior to the start of the treatment).

**Fig. 1** Treatment retention for first starters of each bDMARD using Kaplan–Meier estimation



indicator category). For the stratified analysis of AS and SpA, uveitis, IBD and psoriasis were also adjusted for in the multivariable analyses.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and Stata version 16.1 (StataCorp, College Station, TX, USA).

**Ethics approval**

The study was approved by the Swedish Ethical Review Authority (2016/1986-32).

**Results**

**Drug retention among first-ever users of originator product vs its biosimilar(s)**

In total, 21 443 first-ever starters of the studied drugs were included in the main analyses: 10 354 etanercept treatment courses, 6531 adalimumab, 3724 infliximab and 834 rituximab (see Table 1 and Supplementary Table S3, available at *Rheumatology* online, for the proportion of missing data). During the study period, the use of biosimilar products gradually increased and the choice of drug for new starts varied considerably,

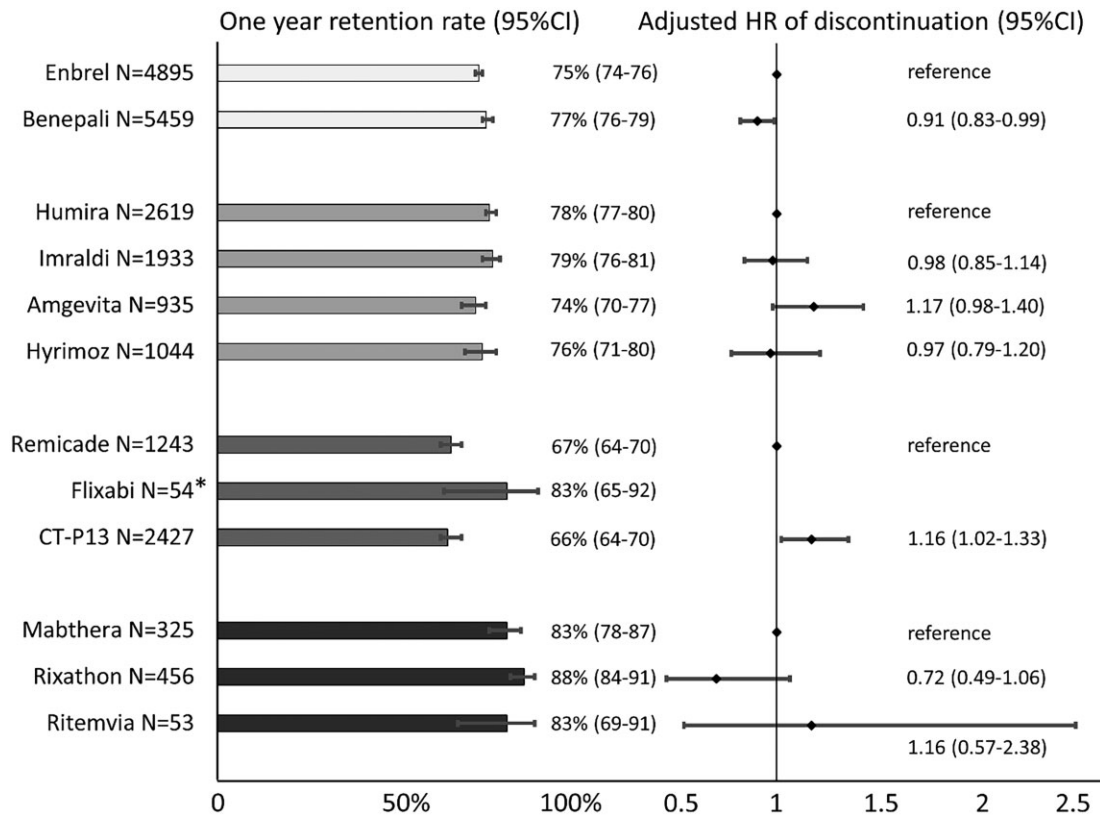
depending primarily on pricing, as seen in Supplementary Fig. S1 (available at *Rheumatology* online).

Patients starting Erelzi ( $n=40$ ), Idacio ( $n=27$ ) and Zessly ( $n=15$ ) were excluded from the analyses, as there were <50 patients in each group.

Within each type of drug [originator plus its biosimilar(s)] we observed no clinically relevant differences in baseline characteristics across the originator and the biosimilars, with the exception of Flixabi (vs Remicade) and Ritemvia (vs Mabthera) (Table 1), which were also the smallest treatment groups. The crude Kaplan–Meier curves of survival on the drug for the different molecules of infliximab, etanercept, adalimumab and rituximab (Fig. 1) indicated no major differences in 1 year treatment retention.

For etanercept, the crude 1 year retention was very similar for the biosimilar Benepali [77% (95% CI 76, 79)] vs the originator Enbrel [75% (95% CI 74, 76)] (Fig. 2). However, both the age- and sex-adjusted [0.91 (95% CI 0.84, 0.98) and the fully adjusted HR [0.91 (95% CI 0.83, 0.99)] for discontinuation suggested a slightly increased retention for Benepali compared with the originator Enbrel. For infliximab, similar crude 1 year retentions were estimated [66% (95% CI 64, 70) vs 67% (95% CI



**Fig. 2** Crude 1 year retention rate and adjusted HR of discontinuation for originators and biosimilars

HR < 1 represents a lower discontinuation rate for the biosimilar compared with the originator. \*HR for Flixabi not estimated due to < 10 discontinuation events. The adjusted HR is adjusted for age, sex, indication, disease duration, line of treatment, year of start of treatment, region, education, concomitant use of csDMARDs and a comorbidity score based on the sum of comorbidities among malignancy, chronic obstructive and interstitial lung disease, heart failure, diabetes, myocardial infarction, kidney, prosthesis and infection.

64, 70)], while the HR for the biosimilar CT-P13 compared with the originator suggested a slightly shorter retention [HR 1.16 (95% CI 1.02, 1.33)]. For adalimumab and rituximab, no statistically significant or clinically relevant differences were observed across originators and biosimilars. HRs for the analyses stratified by indication are shown in Table 2, indicating no large differences across the separate diagnoses. The number of events and results of age- and sex-adjusted Cox regressions are presented in Supplementary Table S4 (available at *Rheumatology* online).

#### Treatment retention following non-medical switch

For the secondary analysis of treatment retention after non-medical switch, we identified 1713 patients switching from Enbrel to Benepali, 558 from Remicade to CT-P13 (Remsima/Inflectra), 137 from Humira to Amgevita and 157 to Hyrimoz and 113 from Mabthera to Ritemvia/Truxima and 247 to Rixathon. Patients switching to Flixabi ( $n = 16$ ), Idacio ( $n = 22$ ), Imraldi ( $n = 46$ ) and Zessly ( $n = 2$ ) were excluded because there were < 50 patients in each of the groups. Baseline characteristics

of the switchers and their individually matched comparator subjects are presented in Supplementary Table S5, available at *Rheumatology* online.

The 1 year retentions and HRs for discontinuation among the patients performing a non-medical switch and their matched controls are presented in Fig. 3. Compared with Fig. 2, the retention among the patients performing a non-medical switch, as well as their comparators, was longer than among the patients starting the corresponding drug for the first time. This is consistent with the patients performing a non-medical switch presumably being on a stable and effective treatment. There were no clinically relevant or statistically significant differences observed within any of the matched cohorts. The number of events and results of age- and sex-adjusted Cox regression are presented in Supplementary Table S6, available at *Rheumatology* online. For the comparison between switchers to Hyrimoz and patients remaining on Humira, the fully adjusted model could not be fitted. Results of a limited model are thus presented, including age, sex, indication, line of treatment, duration and concomitant csDMARD.

TABLE 2 HRs for discontinuation, stratified by indication

Indication	Etanercept				Adalimumab				Infliximab				Rituximab			
	Enbrel	Benepali	Humira	Imraldi	Amgevita	Hyrimoz	Remicade	Flixabi	CT-P13	Mabthera	Rixathon	Ritemvia	Rixathon	Rixathon	Ritemvia	
RA, n	2269	2617	803	724	379	424	509	18	870	299	403	48	403	403	48	
RA, HR (95% CI)	Ref	0.92 (0.81, 0.99)	Ref	0.93 (0.73, 1.18)	1.32 (1.0, 1.72)	0.86 (0.62, 1.19)	Ref	-	1.14 (0.92, 1.41)	Ref	0.73 (0.48, 1.11)	-	0.73 (0.48, 1.11)	0.73 (0.48, 1.11)	-	
PsA, n	1130	1188	691	445	199	243	218	15	508	<5	<5	<5	<5	<5	<5	
PsA, HR (95% CI)	Ref	0.75 (0.6, 0.89)	Ref	1.15 (0.8, 1.55)	1.48 (1.02, 2.14)	1.44 (0.94, 2.20)	Ref	-	1.40 (1.03, 1.89)	Ref	-	-	-	-	-	
AS/SpA, n	917	1111	754	1750	237	257	352	12	700	<5	<5	<5	<5	<5	<5	
AS/SpA, HR (95% CI)	Ref	1.07 (0.88, 1.31)	Ref	0.82 (0.59, 1.13)	0.93 (0.63-1.37)	0.84 (0.51, 1.37)	Ref	-	1.13 (0.87, 1.48)	Ref	-	-	-	-	-	

HR <1 represents a lower discontinuation rate for the biosimilar compared with the originator. HR for strata with <50 exposed are not presented. The HR is adjusted for age, sex, indication, disease duration, line of treatment, region, education, concomitant use of csDMARDs and a comorbidity score based on the number of comorbidities among malignancy, chronic obstructive and interstitial lung disease, heart failure, diabetes, myocardial infarction, kidney, prosthesis and infection.

Sensitivity analysis

Limiting follow-up until 28 February 2020 resulted in very similar results as the main analysis (Table 3).

Discussion

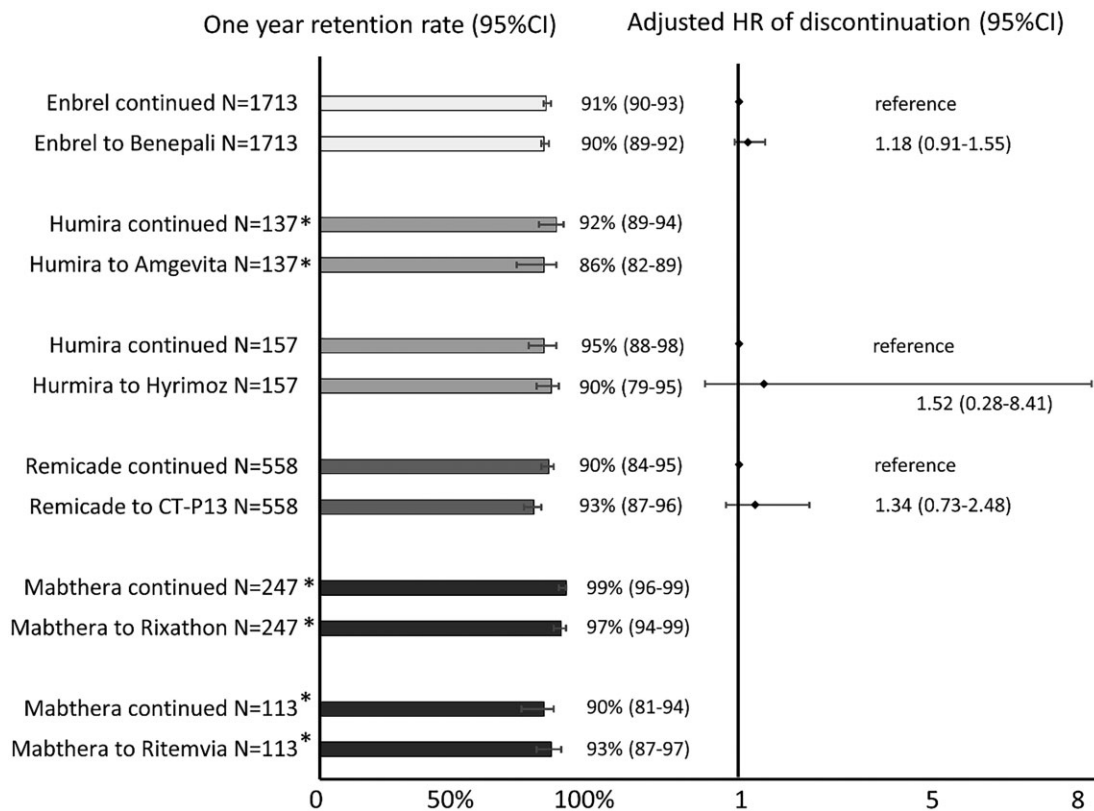
In this study, including patients starting a first-ever treatment with adalimumab, etanercept, infliximab or rituximab or performing a non-medical switch to a biosimilar of one of these drugs, we found no clinically relevant differences in treatment retention for the biosimilars compared with the originator products. There was a signal for slightly better retention for the etanercept biosimilar Benepali compared with Enbrel and for the infliximab originator Remicade compared with CT-P13 (Remsima/Inflectra) for new starters, but this was not statistically significant in analyses of patients performing a non-medical switch. Furthermore, the three biosimilars of adalimumab and the two biosimilars of rituximab had very similar 1 year retentions.

The results of this study are in line with data from RCTs on the equivalence between biosimilars and originator products, both when used as new starts and after switching, for adalimumab [6, 17, 18], etanercept [9], infliximab [19, 20] or rituximab [7, 21]. In several previous observational studies, poorer retention has been reported for biosimilars compared with originators [10-12]. In this study we found no evidence of a placebo effect causing an unfavourable bias for the biosimilars, possibly due to the longer follow-up and the wider use of biosimilars in clinical practice compared with the earlier studies.

Limitations

Some limitations of this study should be mentioned. First, misclassification is likely to occur in register-based studies. However, by ascertaining treatment status from two different registers (for the subcutaneous drugs), we believe that the level of misclassification was low. Second, for some of the comparisons the study may have been underpowered and we set the limit for inclusion at no less than 50 exposed patients in each treatment cohort and at least 10 events in the regression analyses. The results for Flixabi and Ritemvia/Truxima in the main analyses should be interpreted with extra caution due to the relatively small numbers of exposed patients (54 and 53, respectively) and the fact that the baseline characteristics differed somewhat compared with the other drugs of the same type (e.g. in age and length of formal education). Third, rituximab is used relatively often for indications not included in the stratified analyses, and discontinuation is also more difficult to define for rituximab treatment. For this reason, some caution should also be used when extrapolating the results for rituximab to other indications. Fourth, throughout the study period the Swedish Society for Rheumatology

**Fig. 3** Crude 1 year retention and adjusted HR of discontinuation following a non-medical switch to a biosimilar compared with matched controls continuing on the originator



HR <1 represents a lower discontinuation rate for the biosimilar compared with the originator. \*HR for Amgevita, Rixathon and Ritemvia/Truxima not estimated due to <10 discontinuation events. HR for Hyrimoz based on a model with only age, sex, indication, line of treatment, duration and concomitant csDMARD.

sanctioned non-medical switch in well-informed patients with stable treatment and low disease activity. The selection of such a patient group, and the mitigating effect on the nocebo effect, by keeping the patients well informed, would influence the outcomes in favour of switching [22]. However, in clinical practice, the process of non-medical switching has also been fuelled by economic factors, making it impossible to determine to what extent the guidelines of the Swedish Society for Rheumatology have been followed. Thus, although there has been no mandatory national switching strategy in Sweden, within the different counties/regions there has been strong pressure to choose more cost-effective biosimilars/originators for new starts and to perform non-medical switches. How the changes in prices have strongly influenced the choice of drug at new starts is clearly seen in [Supplementary Fig. S1](#), available at *Rheumatology* online. We believe that the gradual and semi-mandatory use of and switch to biosimilars in Sweden has helped to minimize the nocebo effect related to both the patients' and physicians' concerns regarding a change of treatment, but it may also affect the generalizability of the results.

### Strengths

The national coverage and large number of patients included in this study should minimize the potential for bias and allow for extrapolation of the results to other populations. The simultaneous comparison of several biosimilars within the same setting should alleviate the interpretation of a nocebo disadvantage for individual biosimilars compared with their originators, although in this study we did not see such an effect.

### Conclusion

To conclude, in this large study of 21 443 treatment courses comparing biosimilar and originator bDMARDs when used as the first exposure to that specific drug, there was no evidence of any clinically relevant differences in treatment retention. Neither were there any signals of poorer retention following a non-medical switch, including the lack of any obvious nocebo effect. These results support the equivalence of biosimilars and originator products across the available marketed products.



TABLE 3 Treatment retention in sensitivity analysis, restricting follow-up to the pre-COVID-19 pandemic period

Variables	Etanercept			Adalimumab			Infliximab			Rituximab		
	Enbrel	Benepli	Humira	Imraldi	Amgevita	Hyrmoz	Remicade	Flixabi	CT-P13	Mabthera	Rixathon	Ritemvia
Patients, <i>n</i>	4831	4779	2358	1335	638	349	1239	27	2339	318	352	40
Discontinuations, <i>n</i>	1283	1223	486	200	103	12	566	-	1040	57	32	-
% ( <i>n</i> ) due to adverse event	31 (400)	28 (339)	32 (154)	32 (63)	31 (32)	42 (5)	42 (237)	-	35 (364)	28 (16)	31 (10)	-
Person-years	76 026	94 239	24 781	9180	4362	740	26 555	-	40 744	4114	2577	-
Retention rate at 1 year (95% CI)	0.75 (0.74, 0.76)	0.77 (0.76, 0.79)	0.77 (0.75, 0.79)	0.77 (0.73, 0.80)	0.75 (0.70, 0.79)	-	0.65 (0.62, 0.68)	-	0.64 (0.62, 0.66)	0.83 (0.78, 0.87)	0.86 (0.81, 0.90)	-
Crude HR* (95% CI)	Ref	0.88 (0.82, 0.97)	Ref	0.92 (0.78, 1.09)	1.05 (0.85, 1.30)	0.9 (0.50, 1.61)	Ref	-	1.04 (0.94, 1.16)	Ref	0.76 (0.49, 1.19)	-
Adjusted HR (95% CI)	Ref	0.89 (0.81, 0.97)	Ref	1.09 (0.89, 1.34)	1.11 (0.86, 1.42)	1.04 (0.57, 1.90)	Ref	-	1.17 (1.01, 1.35)	Ref	0.64 (0.33, 1.21)	-

Ref, reference.

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## Data availability statement

For reasons related to the legal framework governing the raw data used for this study, individual-level data cannot be freely shared. For requests for study data, please contact the corresponding author.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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