Check for updates

THERAPEUTIC ADVANCES in
Musculoskeletal Disease

Original Research

Counting the costs: a nationwide study on healthcare use following an adalimumab biosimilar switch in >1300 inflammatory arthritis patients

Ther Adv Musculoskelet Dis

2024, Vol. 16: 1–12

DOI: 10.1177/1759720X241289391

© The Author(s), 2024.
Article reuse guidelines: sagepub.com/journals-permissions

Hafsah Nabi, Rikke Ibsen, Michael Ibsen, Jakob Kjellberg, Merete Lund Hetland* and Bente Glintborg*

Abstract

Background: In Denmark, cost savings motivate mandatory biosimilar switches. In 2018, patients switched from originator to biosimilar adalimumab, that is, to GP2017 in Eastern and to SB5 in Western Denmark. However, concerns were raised about additional costs covering, that is, an increased number of outpatient visits due to patient education, treatment monitoring, and patient concerns.

Objectives: To investigate whether the switch led to increased total healthcare costs, defined as costs related to in- and outpatient contacts in hospitals and the primary sector and use of prescription medicine (excluding biological treatment).

Design: Observational cohort study with geographical cluster pseudo-randomization.

Methods: Patients with rheumatoid arthritis, psoriatic arthritis (PsA), and axial spondyloarthritis (AxSpA), who switched were identified in the nationwide DANBIO registry. Total healthcare costs 9 months before and after the switch were captured from the National Patient and Prescription registries. The difference between pre- and post-switch costs was estimated by a generalized estimation equations (GEE) model.

Results: Overall, 1316 patients switched to GP2017 ($n = 621$) or SB5 ($n = 695$). Total healthcare costs were mainly driven by hospital costs. The monthly fluctuations of hospital costs 9 months before and after the switch were largely similar or decreased. In the adjusted analyses (GEE), hospital costs decreased after the switch (by approximately 15%) for GP2017 switchers, especially PsA (estimate = 0.83; 95% CI 0.75–0.92) and AxSpA patients (estimate = 0.85; 0.77–0.93), with no significant changes for SB5 switchers.

Conclusion: We found no increase in total healthcare costs in 9 months following a nationwide mandatory adalimumab originator to biosimilar switch. Our findings were strengthened by similar results for GP2017 and SB5.

Keywords: inflammatory arthritis, biosimilar switches, health-economic outcomes, adalimumab

Received: 1 May 2024; revised manuscript accepted: 20 September 2024.

Correspondence to:
Hafsah Nabi
DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Copenhagen University Hospital Rigshospitalet, Valdemar Hansens Vej 17, Glostrup 2600, Denmark

Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
hafsah.nabi@regionh.dk

Rikke Ibsen
Michael Ibsen
i2minds, Aarhus, Denmark

Jakob Kjellberg
The Danish Centre for Social Science Research, Copenhagen, Denmark

Merete Lund Hetland
Bente Glintborg
DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre of Head and Orthopedics, Copenhagen University Hospital Rigshospitalet, Glostrup, Denmark

Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

*These authors contributed equally.

Introduction

Biological disease-modifying antirheumatic drugs (bDMARDs) have improved the treatment of inflammatory rheumatic diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (AxSpA).[1] Associated medication costs, however, pose a major economic burden, also limiting patient access around the world. During the last decade, the patents of several biologics have expired leading to the marketing of less expensive biosimilars.[2,3] For adalimumab, several biosimilars are available based on

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the Sage and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

results from randomized clinical trials (RCTs) demonstrating non-inferiority among patients switching from the originator to a biosimilar.[4–8] In 2022, the European Union (EU) medicines regulatory network recommended biosimilars to be considered interchangeable meaning that they can replace the reference product or other biosimilars of the same reference product.[9] The use of biosimilars has further been recommended in international guidelines and consensus statements, including the EULAR recommendations for the management of RA.[10,11] This has created financial incentives among stakeholders to implement switching for cost savings (=non-medical switch) and thus potentially increased patient access.[12,13]

Policies for biosimilar uptake vary between European countries and around the world. In Denmark, national guidelines for the use of biological and targeted synthetic DMARDs are issued annually based on a national tender system. This has resulted in several non-medical switches since 2015 and thus a high biosimilar uptake.[14–16]

In the year 2018, the Danish national guidelines mandated the switch of all patients with inflammatory rheumatic diseases treated with originator adalimumab to biosimilar adalimumab based on geographical residence.[14,17] Based on the nationwide tendering process, two different adalimumab biosimilars were available. Patients in Eastern regions (the Capital Region and Region Zealand) were switched to GP2017 (Hyrimoz®) and those in Western regions of Denmark (Region North, Middle, and South) to SB5 (Imraldi®). This strategy provided a unique opportunity for a pseudo-randomized study, and we have previously demonstrated that the switch had no impact on disease activity and treatment retention.[17] The economic benefit was expected to be 34%–49% of the annual adalimumab medication costs (corresponding to approximately 50 million euros annually).[17–19] However, concerns were raised regarding benefits being outweighed by additional costs covering, that is, increased numbers of outpatient visits or hospital contacts due to patient education, treatment monitoring, and patient concerns. This could potentially be driven by factors such as changes in brand name, differences in devices, use of excipients, etc.[19–22]

Health-economic studies of adalimumab switching have mainly focused on the treatment costs of the biologic drug,[18,19] whereas costs associated with healthcare utilization have not yet been addressed. Thus, the primary aim of this study was to investigate whether the switch from originator to either of the adalimumab biosimilars (GP2017/SB5) led to increased total healthcare costs. These were defined as all costs related to in- and outpatient contacts in hospitals and the primary sector and costs of prescription medicine (excluding biological treatment). In addition, it was investigated whether there was a change in healthcare utilization, and if selected patient and disease characteristics affected costs.

Methods

Study design

This was a population-based, observational cohort study with surrogate cluster (i.e., geographical) pseudo-randomization, as previously described in Nabi et al.[17] We emulated a pragmatic trial, in which eligible participants were patients with RA, PsA, or AxSpA monitored in the DANBIO registry and treated with originator adalimumab, who switched to either GP2017 or SB5 according to the national guideline (=switchers). Total healthcare costs before and after switching were estimated with patients serving as their controls in the statistical analyses of healthcare use before and after the switch.

Data sources

Eligible patients were identified in the Danish DANBIO quality registry, which was established in the year 2000, with a prospective follow-up of >95% of all Danish adults with rheumatic disease treated with bDMARDs in routine care.[23,24] For the current study, data in DANBIO were censored by December 2020. By use of the unique civil registration numbers, which each Danish citizen receives at birth, DANBIO data were enriched with patient-level information from the Danish National Patient Registry (DNPR), the Danish Health Insurance Register, and The Danish National Prescription Registry. Thus, we identified comorbidities and utilization of healthcare services, including hospital admissions and duration (hospital days), outpatient visits, primary sector contacts, and prescription medication. The DNPR has virtually complete data on in- and outpatient contacts including information on the ICD-10 diagnosis for the contact.[25] The Danish Health Insurance Register contains information on the settlement

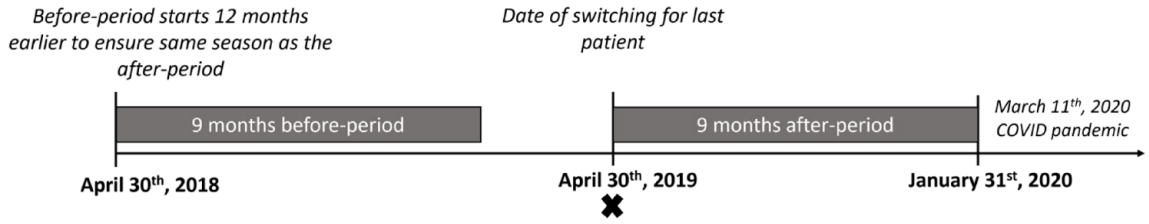


Figure 1. Overview of study periods. The figure illustrates the dates for the last patient in the cohort. The X indicates the index date (date of switch).

and use of health insurance services between the hospital owners (Danish Regions) and providers covered by the health insurance, that is, general practitioners (GPs), practicing specialists, dentists, psychologists, etc. This information was used to estimate the costs of healthcare utilization.[26] The Danish National Prescription registry has individual-level information on all dispensed prescriptions, including ATC-codes[27] (Supplemental Table 1). All findings have been reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[28]

Study population and study period

The study included originator-treated patients with a clinical diagnosis in DANBIO of RA, PsA, or AxSpA, who switched to either biosimilar GP2017 or SB5 between November 1st, 2018 and April 30th, 2019.[17] The baseline (=index date) was the date of the switch. In Denmark, the first COVID-19 lockdown started March 11th, 2020. To minimize the impact of the COVID-19 lockdown on the analyses, the duration of the before- and after-switch periods was restricted to 9 months, that is, the after-switch period ended (for the last patient) on January 31st, 2020 (Figure 1). To ensure that each switcher had comparable calendar seasons in the before- and after-period, the before-period was set to start on the same date the year before (index date for the individual patient minus 12 months; Figure 1).

Outcomes

Primary outcome: Total healthcare costs. Total healthcare costs in the above-defined 9 months of before- and after-switch period (the latter including the index date) were estimated and compared. The cost analysis was divided into costs for hospital contacts, primary sector contacts, and prescription medication. Costs for hospital contacts were calculated according to the activity-based fees (the so-called Diagnosis Related Groups tariffs) and were divided into costs related to (1) the musculoskeletal system and connective tissue (ICD10 codes M00–M99) and (2) other diseases (Supplemental Table 2).[29]

The primary sector included GPs, other specialist doctors, physiotherapists, chiropractors, and foot specialists.

Prescription medicine was grouped into prescribed pain medication (including paracetamol, aspirin, nonsteroid anti-inflammatory drugs (ATC-codes M01A, N02B) and opioids (N02A)) and other medications. Medication costs were estimated according to the defined daily dose (DDD) of medication total costs. Biological drugs were not included, as they are provided directly to the patients through hospitals and pricing information is not publicly available.

The analysis of total healthcare costs before and after the switch was divided into three parts: (1) an estimation of average costs before and after the switch, (2) an analysis of change in costs after (compared to before) the switch, and (3) investigation of whether patient characteristics affected changes. All analyses were stratified according to biosimilar drug and further by indication (RA, PsA, and AxSpA).

Secondary outcome: Healthcare utilization. Due to changes in the registration practice of treatment days for in- and outpatient care in the DNPR from 2019 and onwards, it was not possible to include information regarding healthcare utilization in the hospitals (hospital admissions, hospital days, and outpatient visits).[30] Primary sector healthcare utilization was measured as the number of unique dates with a contact with a GP, other specialist doctor, physiotherapist, chiropractor, foot specialist, or other based on data

from the Danish Health Insurance Register. The use of medication was estimated as DDD. The analysis of utilization before and after the switch was divided into three parts, similar to the cost analysis above.

Clinical variables

Clinical characteristics and DMARD treatment history were retrieved from DANBIO and included the following covariates: age (years), sex (female/male), disease duration (years), use of concomitant methotrexate (MTX; yes/no), treatment duration for originator adalimumab (above/below 6 years), and whether biosimilar adalimumab treatment was withdrawn within 180 days after the switch (yes/no). Previous comorbidities for each patient were identified in the DNPR and coded according to the ICD-10 chapters (21 groups, Supplemental Table 2).

Ethics

The study was approved by the regional GDPR authority (Capital Region Denmark, RH-2015-209, 04145). In Denmark, registry studies neither require patient consent nor ethical approval.[31]

Statistical analyses

All analyses were performed (using SAS V.9.4, SAS Institute Inc) for the overall population stratified by biosimilar drug and further stratified by diagnosis. A p value <0.05 was considered statistically significant. Clinical characteristics and disease activity are presented as medians (interquartile range) for continuous variables and frequencies (percentages) for categorical variables.

Total healthcare costs before and after the switch

Total healthcare costs before and after the switch were estimated by a two-step generalized estimation equations (GEE) regression model[32] with a gamma distribution and a log-link function, where we controlled for age, sex, biosimilar treatment withdrawal within 180 days, treatment duration of originator treatment, and previous comorbidities (Supplemental Table 2). For each patient, previous comorbidities were measured according to the 21 comorbidity groups but excluding musculoskeletal diseases. A GEE model was used since the costs before and after included repeated measures in the same patients and the costs at the two timepoints were correlated.[33]

From the estimates from the GEE model, costs were predicted before and after the switch for a standard patient (defined as being female, 55 years old, not stopped treatment within 180 days, previous duration of originator adalimumab treatment >6 years, and with no comorbidities (excluding musculoskeletal) 12 months before the switch). To estimate whether there were changes in costs after the switch, we included a before–after dummy variable (after = 1) in the GEE model. The estimate for this dummy showed whether there were changes over time (before-minus-after).

For the analyses testing the influence of patient characteristics on changes in total healthcare costs, the statistical model was extended to include interaction terms for the before–after dummy (after = 1) and the variable for the respective patient characteristics (after*independent variable). Thus, it included the following interaction terms: after*sex, after*age, after*previous originator adalimumab treatment, and after*biosimilar withdrawal within 180 days. All estimates reported from the GEE model were on the original scale (the coefficients obtained were exponentiated).

Healthcare utilization before and after the switch

The healthcare utilization (treatment days, number of contacts in the primary sector, and medication usage as DDD) before and after the switch was analyzed using a Poisson regression model similarly including a before–after dummy variable (after = 1) and controlling for the above-mentioned clinical variables. The utilization was predicted before and after according to the same patient characteristics (standard patient) as in the cost analysis.

Results

In total, 1318 patients switched to either GP2017 or SB5 during the inclusion period. Two patients, who were not Danish residents at the index date, were excluded; thus 1316 patients were included in the analyses. Baseline characteristics at the time of switch for both the GP2017 ($n = 621$) and SB5 treatment groups ($n = 695$) are provided in Table 1. In general, patients had established

Table 1. Characteristics of patients who switched from originator adalimumab to biosimilar GP2017 or SB5, overall and stratified by diagnosis.

Clinical characteristics	All patients (*n* = 1316)		GP2017 (*n* = 621)			SB5 (*n* = 695)		
	GP2017	SB5	PsA	RA	AxSpA	PsA	RA	AxSpA
Number of patients (*N*)	621	695	146	213	262	173	253	269
Age[a], years (median, IQR)	55 (44–64)	56 (47–65)	55 (47–62)	63 (56–70)	46 (39–57)	55 (48–63)	64 (57–71)	49 (42–57)
Female, *n* (%)	320 (52)	328 (47)	80 (55)	158 (74)	82 (31)	58 (34)	181 (72)	89 (33)
Disease duration[a], years (median, IQR)	14 (9–20)	14 (9–21)	13 (9–17)	17 (12–23)	12 (8–18)	14 (9–20)	16 (11–24)	12 (8–18)
Concomitant methotrexate[a], *n* (%)	337 (54)	377 (54)	87 (60)	178 (84)	73 (28)	109 (63)	213 (84)	55 (20)
Duration of original bio-treatment before the switch (*n*, %)								
1 year	25 (4)	42 (6)	7 (5)	4 (2)	14 (5)	13 (8)	7 (3)	22 (8)
2–3 years	76 (12)	43 (6)	20 (14)	24 (11)	32 (12)	7 (4)	9 (4)	27 (10)
4–5 years	73 (12)	53 (8)	16 (11)	31 (15)	26 (10)	16 (9)	18 (7)	19 (7)
6+ years	447 (72)	557 (80)	103 (71)	154 (72)	190 (73)	137 (79)	219 (86)	201 (75)
Stopped biosimilar treatment within 180 days (*n*, %)	33 (5)	40 (6)	10 (7)	8 (4)	15 (6)	6 (4)	18 (7)	16 (6)

Source: Reprinted from Nabi et al.[17] with permission.
[a]At baseline.
AxSpA, axial spondyloarthritis; IQR, interquartile range; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

disease (median disease duration 14 years), and the majority of patients (>70%) had been treated with originator adalimumab for >6 years before the index date, as previously described.[17] During 180 days of follow-up, 33 patients (5.3%) in the GP2017 group and 40 patients (5.8%) in the SB5 group withdrew treatment.

Healthcare costs

The hospital costs (i.e., all in- and outpatient contacts) represented the largest share of the total healthcare costs before and after switching, corresponding to approximately 90% of all costs (Table 2). The majority of these were related to diseases of the musculoskeletal system and connective tissue. The average monthly hospital costs 9 months before and after the switch remained largely similar or decreased after the switch (Figure 2). For both treatment groups, an increase was observed in the first month after the switch, which included the date of switching. Healthcare costs in the primary sector fluctuated throughout the 18-month period with no clear pattern (results not shown). The estimated health costs (in €) before and after the switch for a "standard patient" are given in Table 2 for both GP2017 and SB5 treatment cohorts. Results from the fully adjusted regression analyses regarding changes in costs are provided in Table 3. For the GP2017-switch cohort, a statistically significant decrease of approximately 15% in total health costs was observed for PsA (estimate = 0.85; 95% CI (0.78–0.93)) and AxSpA patients (0.86 (0.79–0.94)), mainly driven by reduced hospital costs. On the other hand, there was a 26% increase in costs of prescribed non-pain medication (PsA patients) and a 14% increase in primary sector costs (AxSpA; Table 3). For the SB5-switch cohort, significant changes were seen for costs related to prescription medication in RA patients (estimate = 1.11, 95% CI (1.01–1.23)) and other primary sector costs in AxSpA patients (0.74 (0.56–0.97), Table 3). Overall, sex, age, type of arthritis diagnosis, previous comorbidities, and adalimumab treatment history did not influence

Table 2. Adjusted average healthcare costs for a standard patient for GP2017 and SB5 stratified by diagnosis.

Healthcare service	GP2017						SB5					
	PsA		RA		AxSpA		PsA		RA		AxSpA	
	Health costs (predicted)		Health costs (predicted)		Health costs (predicted)		Health costs (predicted)		Health costs (predicted)		Health costs (predicted)	
	Before (€)	After (€)	Before (€)	After (€)	Before (€)	After (€)	Before (€)	After (€)	Before (€)	After (€)	Before (€)	After (€)
Hospital costs												
Musculoskeletal system and the connective tissue	7.018	5.880	7.311	8.058	7.142	6.641	7.696	8.003	7.603	7.851	6.877	7.767
Other secondary sector treatment costs	824	614	313	310	520	1.070	446	500	442	677	640	476
Hospital total treatment costs	8.048	6.236	7.446	8.051	8.010	7.534	7.903	8.054	7.799	8.357	7.565	8.026
Primary sector												
General practitioner	123	103	116	98	94	91	111	111	120	120	112	105
Specialist	70	124	81	56	58	108	56	81	40	40	81	54
Physiotherapist, chiropractor, and foot specialist	296	291	204	247	173	226	435	523	376	382	299	206
Other	52	48	47	42	31	80	58	43	40	41	56	51
Primary sector total costs	542	580	451	437	353	524	595	643	565	563	549	427
Prescription medication												
Pain medication (DDD)	59	42	18	18	14	30	46	36	29	29	58	43
Not pain medication (DDD)	209	234	128	130	172	312	255	223	124	192	86	74
Prescription medication total costs (DDD)	273	275	148	151	186	335	311	274	149	220	142	110
Total healthcare costs	8.856	7.083	8.048	8.662	8.603	8.346	8.859	9.013	8.511	9.110	8.103	8.378

[a]Adjusted average healthcare costs, given in euro (€), estimated for a "standard patient" defined as a 55-year-old female, with no previous comorbidities, with previous duration of originator adalimumab >6 years and not withdrawn biosimilar GP2017/SB5 within 180 days.
AxSpA, axial spondyloarthritis; DDD, defined daily dose; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

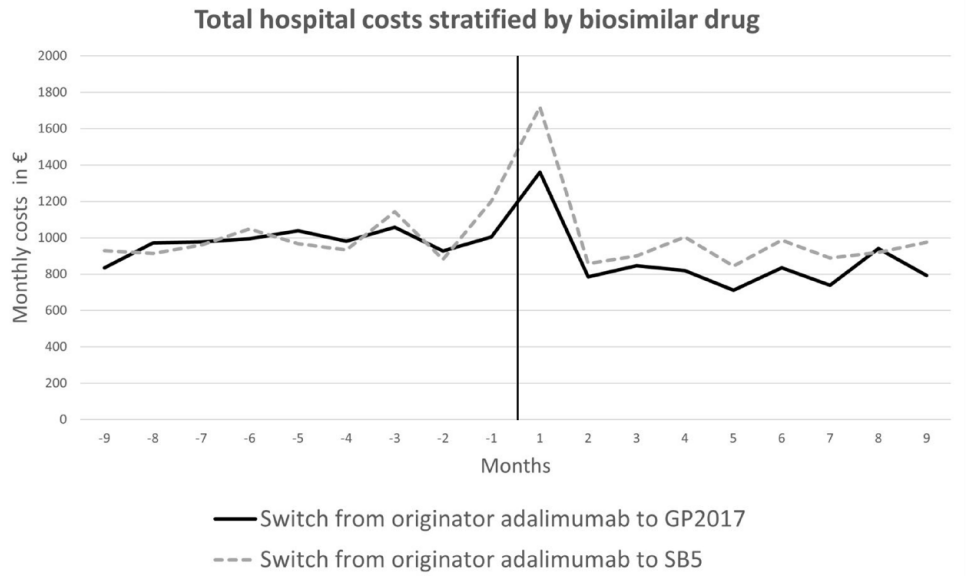


Figure 2. Monthly average hospital costs per patient 9 months before and after the switch from originator to biosimilar adalimumab. The black dotted line indicates the date of the switch. *y*-axis: mean cost per patient per month (unadjusted). Number of patients in each biosimilar treatment group: GP2017 ($n = 621$) and SB5 ($n = 695$).

changes in healthcare costs, whereas type of biosimilar drug (GP2017 or SB5) had a significant impact. Results were similar in the total treatment cohort (Supplemental Table 3) and stratified by diagnosis (results not shown).

Healthcare utilization before and after the switch

Results from the analyses of healthcare utilization in the primary sector and prescribed medication before and after the switch are given in Supplemental Tables 4 to 5. There were slight fluctuations in utilization across treatment groups with no clear pattern in relation to the switch.

Discussion

In this nationwide study of >1300 Danish real-world patients with inflammatory arthritis, we investigated the health-economic consequences of switching from originator to biosimilar adalimumab (GP2017 or SB5, based on geographical residence) following a mandatory nationwide guideline. Overall, we found no negative impact of the switch on total healthcare costs on a range of healthcare services (hospital contacts, primary sector visits, and prescribed medication) during a 9-month period. On the contrary, when stratified by biosimilar drug, we found a significant decrease of approximately 15% in total healthcare costs after the switch mainly for GP2017 switchers with PsA or AxSpA.

Several studies, both RCTs and real-world observational studies, have suggested biosimilar switching to have no negative impact on treatment effect, effectiveness, safety, and immunogenicity.[1,5,7,10,17,34] However, the use of biosimilars varies around the world with a significantly lower uptake in, for example, the United States, Japan, and Canada compared to some European countries.[35] In Denmark, the biosimilar uptake is high due to mandated switch procedures and national treatment guidelines that favor the use of biosimilars.[15,16,18,36] Although the use of biosimilars may significantly reduce the financial burden of bDMARDs on the healthcare system,[13] the full impact of biosimilar switching on healthcare utilization and the associated costs is complex to assess.[19] Most previous studies have focused on the direct drug costs and found substantial savings (up to 83% for adalimumab),[18] but it is important to consider the costs associated with healthcare utilization (e.g., additional consultations).[37] Thus, it is reassuring that we found no increased healthcare costs following this nationwide mandatory adalimumab switch.

Table 3. Estimated healthcare costs after versus before switch stratified by diagnosis and biosimilar drug.

	PsA		RA		AxSpA	
	After		After		After	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
GP2017						
Hospital costs						
Musculoskeletal system and the connective tissue	**0.77 (0.69–0.85)**	<0.001	0.92 (0.79–1.05)	0.22	**0.82 (0.76–0.89)**	<0.001
Other hospital costs	0.98 (0.68–1.41)	0.92	1.25 (0.82–1.90)	0.29	**1.73 (1.15–2.60)**	0.008
Total hospital costs	**0.83 (0.75–0.92)**	<0.001	0.99 (0.86–1.14)	0.87	**0.85 (0.77–0.93)**	<0.001
Primary sector						
General practitioner	0.94 (0.79–1.11)	0.46	**0.87 (0.77–0.99)**	0.04	1.14 (1.00–1.31)	0.06
Specialist	1.04 (0.72–1.49)	0.85	1.02 (0.76–1.37)	0.91	**1.58 (1.11–2.25)**	0.01
Physiotherapist, chiropractor, and foot specialist	1.05 (0.82–1.35)	0.71	**1.16 (1.03–1.30)**	0.01	1.05 (0.87–1.27)	0.62
Other	0.93 (0.73–1.19)	0.58	0.89 (0.72–1.10)	0.27	**0.73 (0.59–0.90)**	0.003
Primary sector total costs	1.00 (0.87–1.16)	0.97	1.02 (0.93–1.12)	0.64	**1.14 (1.00–1.29)**	0.04
Prescription medication						
Pain medication	0.96 (0.73–1.27)	0.77	0.92 (0.74–1.14)	0.43	1.02 (0.84–1.25)	0.83
Not pain medication	**1.26 (1.07–1.48)**	0.005	1.05 (0.91–1.23)	0.49	1.03 (0.88–1.21)	0.69
Prescription medication total costs	**1.20 (1.04–1.39)**	0.01	1.04 (0.91–1.19)	0.56	1.04 (0.90–1.19)	0.62
Total healthcare costs	**0.85 (0.78–0.93)**	<0.001	0.99 (0.87–1.13)	0.89	**0.86 (0.79–0.94)**	<0.001
SB5						
Hospital costs						
Musculoskeletal system and the connective tissue	1.05 (0.96–1.15)	0.26	1.00 (0.94–1.07)	0.99	1.00 (0.93–1.07)	0.92
Other hospital costs	1.02 (0.73–1.45)	0.89	1.08 (0.71–1.64)	0.71	0.95 (0.54–1.67)	0.86
Total hospital costs	1.03 (0.95–1.13)	0.46	1.00 (0.93–1.08)	0.97	1.01 (0.91–1.12)	0.92
Primary sector						
General practitioner	0.96 (0.83–1.11)	0.54	0.97 (0.87–1.07)	0.49	1.01 (0.89–1.16)	0.84
Specialist	1.02 (0.58–1.81)	0.93	0.94 (0.71–1.26)	0.69	0.94 (0.60–1.46)	0.78
Physiotherapist, chiropractor, and foot specialist	0.98 (0.83–1.17)	0.84	1.09 (0.98–1.21)	0.10	0.95 (0.86–1.04)	0.26
Other	0.87 (0.74–1.03)	0.11	0.97 (0.86–1.11)	0.68	**0.74 (0.56–0.97)**	0.03
Primary sector total costs	0.99 (0.88–1.12)	0.90	1.02 (0.96–1.10)	0.49	0.94 (0.86–1.02)	0.15
Prescription medication						
Pain medication (DDD)	0.92 (0.83–1.02)	0.10	0.98 (0.88–1.10)	0.76	0.98 (0.85–1.12)	0.73
Not pain medication (DDD)	1.02 (0.93–1.11)	0.74	**1.13 (1.02–1.26)**	0.02	0.96 (0.87–1.06)	0.40
Prescription medication total costs (DDD)	1.00 (0.93–1.08)	0.95	**1.11 (1.01–1.23)**	0.03	0.96 (0.88–1.04)	0.31
Total healthcare costs	1.03 (0.95–1.11)	0.48	1.01 (0.94–1.08)	0.85	1.00 (0.91–1.10)	0.99

[a]Results of the GLM model (after = 1) adjusted for sex, age, number of years treated with originator drug (>6 years = 1), stopped the medication within 180 days (yes–no), and comorbidity (number of WHO 21 chapters excluding WHO 13 ICD-10 M (musculoskeletal diseases)). Values in bold indicate statistically significant results.
AxSpA, axial spondyloarthritis; DDD, defined daily dose; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Previous studies exploring healthcare costs following a biosimilar switch have mainly been done for infliximab and etanercept[19]; among these, only a few have included a before–after switch period or compared to patients, who did not switch. A European survey among rheumatology specialists found increased use of healthcare services (visits and procedures) at 0–3 and 4–6 months in >1200 patients who switched to etanercept biosimilar. The study mainly included patients with stable RA disease and compared switchers versus non-switchers.[38] The study was limited by the survey format and did not take comorbidities or seasonal variations into account. Other infliximab and etanercept biosimilar switch studies based on medical records and registry data report either no major changes or marginal increases in the number of outpatient visits 6 months post-switch.[39–41] However, these experiences cannot be readily extrapolated to adalimumab for several reasons: the administration routes may differ (intravenous for infliximab), the drugs may be used by patients with different demographic and disease characteristics, and the perception of biosimilars among healthcare professionals/patients may change over time.[42,43]

In this study, we provide data regarding the average healthcare costs and utilization before and after the switch for both GP2017 and SB5 and further stratified by diagnosis. For both biosimilars, the costs either remained unchanged or decreased compared to before the switch throughout the 9 months of the after-period. The initial increase in hospital costs after the switch is likely due to consultations in relation to the switching—a pattern previously seen also for etanercept.[39] Stratified by drug, we found reduced overall healthcare costs for GP2017 switchers. A difference between GP2017 and SB5 was supported by the test of patient characteristics associated with changes in healthcare costs where the type of adalimumab biosimilar drug had a significant influence. We have previously demonstrated higher 1-year treatment retention and disease remission rates among GP2017 switchers compared to SB5.[17] This may be due to changes in the device; however, geographical differences or residual confounding could potentially impact these results, as previously discussed in Nabi et al.[17] Patients were mainly informed about the switch by nurses in the outpatient clinics, and no specific patient material was distributed. Differences in the transition or communication strategy in the different regions of Denmark should be considered, but we have no data to explore this further. Also, neither patients nor healthcare professionals were blinded by the switch, and the presence of a nocebo effect due to negative expectations may potentially have affected outcomes.[22,44–46]

The study is based on data from DANBIO linked with other Danish nationwide registries. Strengths include the nationwide prospective follow-up, high data completeness of the registries, and a high (89%) compliance to the nationwide switch guideline,[17] which provides a unique opportunity for monitoring outcomes in large cohorts. It is also a strength that patients served as their controls in the statistical analyses of use before and after the switch. Patients were switched according to their geographical residence; thus, for the comparisons of GP2017 versus SB5, confounding by indication is expected to be minimal. A limitation is the lack of adalimumab medication costs in the estimates. The drug prices fluctuated over time and were not publicly available due to the Danish tender process. Others have, however, reported a reduction in adalimumab costs by up to 80% when switching from an originator to a biosimilar.[18,47] Our study focused on costs in the healthcare sector. It was beyond the scope to investigate patient-related costs or indirect costs (productivity loss, etc.).

Conclusion

In conclusion, we found no increased total healthcare costs in 9 months following a nationwide mandatory adalimumab originator to biosimilar switch. Our findings were strengthened by similar results for GP2017 and SB5.

Declarations

Ethics approval and consent to participate

The study has been approved by the regional GDPR authority (Capital Region Denmark, RH-2015-209, 04145). In Denmark, registry studies neither require patient consent nor ethical approval.

Consent for publication

Not applicable.

Author contributions

Hafsah Nabi: Conceptualization; Formal analysis; Investigation; Methodology; Project

administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Rikke Ibsen: Conceptualization; Data curation; Formal analysis; Methodology; Software; Visualization; Writing – review & editing.

Michael Ibsen: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Software; Writing – review & editing.

Jakob Kjellberg: Conceptualization; Methodology; Resources; Writing – review & editing.

Merete Lund Hetland: Conceptualization; Investigation; Data curation; Funding acquisition; Methodology; Project administration; Supervision; Writing – review & editing.

Bente Glintborg: Conceptualization; Investigation; Data curation; Funding acquisition; Methodology; Project administration; Supervision; Writing – review & editing.

Acknowledgements
We are thankful to all patients and Danish departments of rheumatology for reporting to the DANBIO registry. Also, the work of IT consultants Niels Steen Krogh and Zitelab Aps, who extracted data from DANBIO is acknowledged. The authors acknowledge AbbVie for supporting the work. This work was presented as a poster at the EULAR Congress 2023.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research grant from AbbVie, who had no on the data collection, statistical analyses, or decision to submit.

Competing interests
Hafsah Nabi: Research grant from AbbVie and Sandoz.

Merete Lund Hetland: AbbVie, Biogen, BMS, Celtrion, Eli Lilly Denmark A/S, Janssen Biologics B.V, Lundbeck Fonden, MSD, Pfizer, Roche, Samsung Bioepis, Sandoz. Co-chair EuroSpA, which generates real-world evidence of treatment of psoriatic arthritis and axial spondyloarthritis based on secondary data and is partly funded by Novartis.

Bente Glintborg: BMS, Pfizer, Sandoz (research grants) Furthermore, chair of the steering committee of the Danish Rheumatology Quality Registry (DANBIO), which receives public funding from the hospital owners and funding from pharmaceutical companies.

Remaining authors: none declared.

Availability of data and materials
In this study, data are combined from several Danish nationwide registries and hosted at Statistics Denmark. Data cannot be shared publicly due to requirements of the involved register holders and the general data protection regulation, to protect the privacy of individuals.

Patient and public involvement
Thank you to the patient partners within the DANBIO steering committee.

ORCID iD
Hafsah Nabi https://orcid.org/0000-0001-6331-7927

Supplemental material
Supplemental material for this article is available online.

References
1. Schulze-Koops H and Skapenko A. Biosimilars in rheumatology: a review of the evidence and their place in the treatment algorithm. *Rheumatology* 2017; 56(Suppl_4): iv30–iv48.
2. 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(1): 198–206.
3. Smolen JS, Goncalves J, Quinn M, et al. Era of biosimilars in rheumatology: reshaping the healthcare environment. *RMD Open* 2019; 5(1): e000900.
4. Weinblatt ME, Baranauskaite A, Niebrzydowski J, et al. Phase III randomized study of SB5, an adalimumab biosimilar, versus reference adalimumab in patients with moderate-to-severe rheumatoid arthritis. *Arthritis Rheumatol* 2018; 70(1): 40–48.
5. Cohen SB, Alonso-Ruiz A, Klimiuk PA, et al. Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: results from the phase III randomised VOLTAIRE-RA equivalence study. *Ann Rheum Dis* 2018; 77(6): 914–921.

6. Genovese MC, Glover J, Greenwald M, et al. FKB327, an adalimumab biosimilar, versus the reference product: results of a randomized, Phase III, double-blind study, and its open-label extension. *Arthritis Res Ther* 2019; 21(1): 1–12.
7. Zhao S, Chadwick L, Mysler E, et al. Review of biosimilar trials and data on adalimumab in rheumatoid arthritis. *Curr Rheumatol Rep* 2018; 20(10): 1–10.
8. Blauvelt A, Lacour JP, Fowler JF, et al. Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches. *Br J Dermatol* 2018; 179(3): 623–631.
9. Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU, www.ema.europa.eu/contact (2022, accessed 16 September 2024).
10. Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis* 2018; 77(2): 165–174.
11. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023; 82(1): 3–18.
12. Troein P, Newton M and Scott K. The impact of biosimilar competition in Europe, https://ec.europa.eu/health/system/files/2021-01/biosimilar_competition_en_0.pdf (2020, accessed 16 September 2024).
13. Kvien TK, Patel K and Strand V. The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems. *Semin Arthritis Rheum* 2022; 52: 151939.
14. Medicinrådet. Implementation of biosimilar Adalimumab, Denmark [Internet], https://medicinraadet.dk/media/svab0lxx/medicinraadets-vurdering-af-ibrugtagning-af-biosimilaer-adalimumab-version-10_adlegacy.pdf (2018, accessed 16 September 2024).
15. Jensen TB, Bartels D, Sædder EA, et al. The Danish model for the quick and safe implementation of infliximab and etanercept biosimilars. *Eur J Clin Pharmacol* 2020; 76(1): 35–40.
16. Glintborg B, Loft AG, Omerovic E, et al. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. *Ann Rheum Dis* 2019; 78(2): 192–200.
17. Nabi H, Georgiadis S, Loft AG, et al. Comparative effectiveness of two adalimumab biosimilars in 1318 real-world patients with inflammatory rheumatic disease mandated to switch from originator adalimumab: nationwide observational study emulating a randomised clinical trial. *Ann Rheum Dis* 2021; 80(11): 1400–1409.
18. Jensen TB, Kim SC, Jimenez-Solem E, et al. Shift from adalimumab originator to biosimilars in Denmark. *JAMA Intern Med* 2020; 180(6): 902–903.
19. Hillhouse E, Mathurin K, Bibeau J, et al. The economic impact of originator-to-biosimilar non-medical switching in the real-world setting: a systematic literature review. *Adv Ther* 2022; 39(1): 455–487.
20. Kristensen LE, Alten R, Puig L, et al. Non-pharmacological effects in switching medication: the Nocebo effect in switching from originator to biosimilar agent. *BioDrugs* 2018; 32(5): 397–404.
21. The Lancet Rheumatology. Biosimilars and the era of interchangeability. *Lancet Rheumatol* 2023; 5(9): e495.
22. Rezk MF and Pieper B. Treatment outcomes with biosimilars: be aware of the Nocebo effect. *Rheumatol Ther* 2017; 4(2): 209–218.
23. Ibfelt EH, Sørensen J, Jensen D V, et al. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. *Clin Epidemiol* 2017; 9: 627.
24. Hetland ML. DANBIO—powerful research database and electronic patient record. *Rheumatology* 2011; 50(1): 69–77.
25. Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015; 7: 449.
26. Sahl Andersen J, De Fine Olivarius N and Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011; 39(7): 34–37.
27. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, et al. Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012; 4(1): 303–313.
28. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational

Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61(4): 344–349.

29. DRG-takster 2019—Sundhedsdatastyrelsen, https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2019 (2019, accessed 16 September 2024).
30. Sundhedsdatastyrelsen. Datakvalitetsrapport om LPR 2019-overgangen fra LPR2 til LPR3, https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sygdomme-laegemidler-og-behandlinger/landspatientregisteret/landspatientregisteret-moderniseres (2020, accessed 16 September 2024).
31. Overblik over anmeldelsespligten | De Videnskabsetiske Komitéer, https://videnskabsetik.dk/ansoegning-til-etisk-komite/overblik-over-anmeldelsespligten (2024, accessed 16 September 2024).
32. Buntin MB and Zaslavsky AM. Too much ado about two-part models and transformation? Comparing methods of modeling Medicare expenditures. *J Health Econ* 2004; 23(3): 525–542.
33. Wang M. Generalized estimating equations in longitudinal data analysis: a review and recent developments. *Adv Stat* 2014; 2014(1): 303728.
34. Thomas D, Strand V, Cornes P, et al. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016; 75(6): 974–982.
35. Alnaqbi KA, Bellanger A, Brill A, et al. An international comparative analysis and roadmap to sustainable biosimilar markets. *Front Pharmacol* 2023; 14: 1188368.
36. 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(8): 1426–1431.
37. Liu Y, Yang M, Garg V, et al. Economic impact of non-medical switching from originator biologics to biosimilars: a systematic literature review. *Adv Ther* 2019; 36(8): 1851–1877.
38. Tarallo M, Onishchenko K and Alexopoulos ST. Costs associated with non-medical switching from originator to biosimilar etanercept in patients with rheumatoid arthritis in the UK. *J Med Econ* 2019; 22(11): 1162–1170.
39. Glintborg B, Ibsen R, Bilbo REQ, et al. Does a mandatory non-medical switch from originator to biosimilar etanercept lead to increase in healthcare use and costs? A Danish register-based study of patients with inflammatory arthritis. *RMD Open* 2019; 5(2): e001016.
40. Glintborg B, Sørensen J and Hetland ML. Does a mandatory non-medical switch from originator to biosimilar infliximab lead to increased use of outpatient healthcare resources? A register-based study in patients with inflammatory arthritis. *RMD Open* 2018; 4(2): e000710.
41. Gibofsky A, Skup M, Yang M, et al. Short-term costs associated with non-medical switching in autoimmune conditions. *Clin Exp Rheumatol* 2019; 37(1): 97–105.
42. Leonard E, Wascovich M, Oskouei S, et al. Factors affecting health care provider knowledge and acceptance of biosimilar medicines: a systematic review. *J Manag Care Spec Pharm* 2019; 25(1): 102–112.
43. Gasteiger C, Lobo M, Dalbeth N, et al. Patients' beliefs and behaviours are associated with perceptions of safety and concerns in a hypothetical biosimilar switch. *Rheumatol Int* 2021; 41(1): 163–171.
44. 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(1): 60–68.
45. Fleischmann R, Jairath V, Mysler E, et al. Nonmedical switching from originators to biosimilars: does the Nocebo effect explain treatment failures and adverse events in rheumatology and gastroenterology? *Rheumatol Ther* 2020; 7(1): 35–64.
46. 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(10): 952–959.
47. Coghlan J, He H and Schwendeman AS. Overview of Humira® biosimilars: current European landscape and future implications. *J Pharm Sci* 2021; 110(4): 1572–1582.

Visit Sage journals online journals.sagepub.com/home/tab

Sage journals