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ORIGINAL RESEARCH

Infliximab biosimilar-to-biosimilar switching in patients with inflammatory rheumatic disease: clinical outcomes in real-world patients from the DANBIO registry

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ABSTRACT

Objective Successful uptake of biosimilars in rheumatology is limited by lack of real-world evidence regarding effectiveness of biosimilar-to-biosimilar switching. We investigated infliximab biosimilars CT-P13-to-GP1111 switching among patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (AxSpA).

Methods Observational cohort study from the DANBIO registry. Patients were classified as originator-naïve or originator-experienced. Retention rates of 1-year GP1111 treatment were explored (Kaplan-Meier). We identified baseline factors (at the time of switch) associated with withdrawal of GP1111 (multivariable Cox-regression analyses with HRs including originator treatment history). Changes in subjective and objective measures of disease activity 4 months before and after the switch were assessed in individual patients.

Results Of 1605 patients (685 RA, 314 PsA and 606 AxSpA, median disease duration was 9 years, 37% in Clinical Disease Activity Index/Ankylosing Spondylitis Disease Activity Score remission), 1171 were originator-naïve. Retention rates at 1-year were 83% (95% CI: 81% to 85%) and 92% (95% CI: 90% to 95%) for the originator-naïve and originator-experienced, respectively. GP1111 retention rates were higher in originator-experienced compared to originator-naïve with RA (HR=0.4 (95% CI: 0.2 to 0.7)) and PsA (HR=0.2 (95% CI: 0.1 to 0.8)), but not significantly for AxSpA: HR=0.6 (95% CI: 0.3 to 1.2). Lower disease activity was associated with higher retention. Changes in disease activity preswitch and postswitch were close to zero.

Conclusion This real-world observational study of more than 1600 patients with inflammatory arthritis showed high 1-year retention following a nationwide infliximab biosimilar-to-biosimilar switch. Retention was higher in originator-experienced and in patients with low disease activity, suggesting outcomes to be affected by patient-related rather than drug-related factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The lack of randomised trials and real-world evidence regarding outcomes following switch from one biosimilar to a second of the same originator limits the uptake of biosimilars in routine care rheumatology settings.

WHAT THIS STUDY ADDS

⇒ In this observational cohort study, we explored 1 year outcomes among more than 1600 patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis following a nationwide infliximab biosimilar-to-biosimilar switch (CT-P13 to GP1111).

⇒ Treatment retention at 1 year was high in both groups, with lower withdrawal rates among originator-experienced and patients with lower disease activity at the time of switch.

⇒ Disease activity in individual patients 4 months before and after switch was stable with no clinically relevant differences.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A mandatory infliximab biosimilar-to-biosimilar switch was well tolerated by patients. Retention was influenced by patient-related factors.

Biosimilar drugs are highly similar versions of the originator biologic disease-modifying antirheumatic drugs (bDMARDs). Their use is motivated by cost savings.[1] Different switch scenarios are emerging with increasing availability of biosimilars, including switching from

one biosimilar to a second of the same originator,[2] in this paper termed *biosimilar-to-biosimilar (B2B)-switching*.

For the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (AxSpA) evidence regarding infliximab B2B-switching is limited.[1 3 4] Randomised clinical trials (RCTs) have mainly investigated the efficacy and safety of switching from originator infliximab to a corresponding biosimilar.[2 5–8] Real-world evidence supporting infliximab B2B-switches stems from a few minor studies in, for example, psoriasis and inflammatory bowel disease (IBD).[2 9–12] Concerns regarding B2B-switches relate to effectiveness, safety and immunogenicity.[1 13] Previous studies on originator-to-biosimilar switching in real-world patients have indicated an impact of patient-related factors (eg, treatment history and disease activity at the time of switching) on treatment outcomes[14–17]; however their role remains unclear in B2B-switching. As recommended in the consensus document by Kay *et al*,[18] outcomes of B2B-switching should be assessed in real-world registries.

The uptake of biosimilars is high in Denmark.[19 20] Mandatory nationwide switches of, for example, infliximab have been conducted: first from originator to CT-P13 (year 2015), followed by switch to GP1111 (year 2019) in accordance with Danish guidelines.[21] Clinical outcomes were prospectively monitored in the nationwide clinical registry, DANBIO,[22] providing a unique opportunity for the study of real-world effectiveness following B2B-switching.

In this study, we aimed to investigate the effectiveness of infliximab biosimilar CT-P13-to-GP1111 switching among patients with RA, PsA and AxSpA, including those patients who had previously switched from originator to CT-P13 (originator-experienced) and those who were originator-naïve. Furthermore we aimed to identify factors associated with retention to treatment following the switch.

METHODS

Study design

Observational cohort study. More than 95% of adults with inflammatory rheumatic disease treated with bDMARDs in routine care are prospectively followed in DANBIO.[22 23] Using civil registration numbers, patient-level information from DANBIO was enriched with previous comorbidities and vital status from The Danish National Patient Registry, and The Danish Civil Registry, respectively (online supplemental table S1).[24 25]

Study population

We included patients with a clinical diagnosis of RA, PsA or AxSpA, who performed a B2B-switch from CT-P13 to GP1111 between 1 April 2019 and 1 February 2020 (date of switching=baseline). Patients were divided into two subgroups: *originator-naïve* and *originator-experienced* (figure 1).

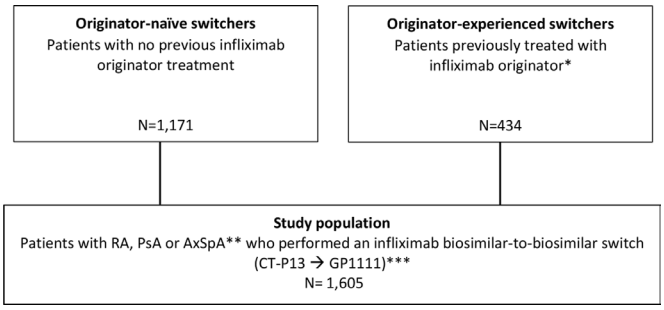


Figure 1 Study population and definition of the two subgroups according to originator infliximab treatment history. *Switched to CT-P13 in the period 1 May 2015 to 1 March 2016. A time gap of 0–120 days between stop of originator and start of biosimilar was allowed to comply with registration practice.**Based on following International Classification of Diseases (ICD)-10 codes: For RA: M05.9, M06.0, M06.9, M13.0, for PsA: M073.A, M073.B, M46.8 in combination with M07.3 and for AxSpA: M45.9, M46.1, M46.8, M46.9, also M45.9 and M46.8 in combination with M02.9, M07.2, M07.4, M07.5 and/or H20.0. Also minimum one visit in DANBIO after 1 April 2019, and aged ≥18 years at the time of treatment start with a biologic disease-modifying antirheumatic drug (bDMARD). ***Switched to GP1111 in the period 1 April 2019 to 1 February 2020. AxSpA, axial spondyloarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Outcomes

The primary outcome was 1-year GP1111 treatment retention in the two subgroups, overall and stratified by indication (RA, PsA and AxSpA). The key secondary outcome was baseline factors associated with GP1111 treatment withdrawal for both groups combined (stratified by indication). Other secondary outcomes included reasons for withdrawal and changes in disease activity 4 months before and after the switch (stratified by indication).

Follow-up

Patients were followed-up for 1 year after baseline. Treatment duration was the number of days each patient maintained treatment with GP1111, until withdrawal (=first missed dose irrespective of reason), death, lost to follow-up or data-cut, whichever came first. Temporary interruptions of less than 3 months' duration (eg, due to surgery, infections) were disregarded. Reasons for withdrawal were identified according to predefined categories in DANBIO.

Approvals

Danish registry studies neither require patient consent nor ethical approval. The study was approved by the Danish Data Protection Agency (RH-2015–209, 04145). Data from DANBIO was obtained through the Danish Rheumatologic Quality Registry (RKKP DANBIO-2021-07-09).

Statistical analysis

All statistical analyses were conducted using R (V.3.6.1).[26] P values<0.05 were considered statistically significant.

Table 1 Characteristics of originator-naïve and originator-experienced switchers at the time of GP1111 switch, stratified by indication

	Originator-naïve switchers, N=**1171**			**Originator-experienced switchers, N=434**		
	RA*	**PsA**	**AxSpA**	**RA***	**PsA**	**AxSpA**
Number of patients, n	482	244	445	203	70	161
Female, n (%)	327 (68)	127 (52)	155 (35)	147 (72)	26 (37)	36 (22)
Age, years	59 (47–67)	51 (40–58)	42 (32–51)	66 (55–74)	56 (50–65)	51 (43–58)
Disease duration, years	7 (4–14)	7 (4–12)	4 (3–7)	20 (14–27)	16 (12–25)	18 (12–25)
0–5 years, n (%)	178 (38)	81 (36)	266 (63)	0 (0)	<5	0 (0)
>5 years, n (%)	291 (62)	142 (64)	159 (37)	194 (100)	67 (99)	159 (100)
BMI, kg/m^2	25.2 (22.2–29.4)	28.1 (23.8–31.2)	26.1 (23.1–28.7)	24.3 (21.9–28.2)	26.3 (23.8–28.7)	25.2 (22.8–27.8)
Current smoking, n (%)	119 (25)	45 (19)	125 (28)	42 (21)	17 (24)	49 (31)
Year of originator treatment start						
2000–2004, n (%)	–	–	–	51 (25)	6 (9)	28 (17)
2005–2009, n (%)				105 (52)	44 (63)	93 (58)
2010–2015, n (%)				47 (23)	20 (28)	40 (25)
Prior originator treatment duration, years	–	–	–	8 (6–11)	7 (5–9)	8 (6–10)
Prior CT-P13 treatment duration, years	1 (1–3)	1 (1–3)	1 (1–3)	4 (4–4)	4 (4–4)	4 (4–4)
Concomitant MTX, n (%)	354 (73)	134 (55)	52 (12)	163 (81)	48 (69)	33 (21)
Prior non-infliximab bDMARD treatments, n (%)						
0	324 (67)	163 (67)	314 (70)	134 (66)	51 (73)	113 (70)
1	84 (17)	48 (20)	65 (15)	37 (18)	11 (16)	25 (16)
≥2	74 (15)	33 (14)	66 (15)	32 (16)	8 (11)	23 (14)
Visits during 1 year follow-up	3 (2–6)	3 (2–7)	3 (2–7)	3 (2–6)	2 (2–5)	3 (2–6)
Disease activity						
In DAS28/ASDAS remission†, n (%)	215 (45)	135 (55)	128 (29)	123 (61)	43 (61)	56 (35)
In CDAI/ASDAS remission‡, n (%)	193 (40)	102 (42)	128 (29)	86 (42)	27 (39)	56 (35)
CRP, mg/L	3 (1–6)	2 (1–4)	2 (1–4)	2 (1–3)	2 (1–4)	2 (1–3)
DAS28	2.3 (1.8–3.2)	2.1 (1.7–2.9)	–	1.9 (1.4–2.4)	2.0 (1.6–2.5)	–
CDAI	5.6 (2.3–9.7)	5.2 (2.0–9.5)	–	2.9 (1.4–5.8)	4.1 (2.1–7.4)	–
BASDAI, mm	–	–	27.5 (12.7–51.2)	–	–	22.7 (6.3–36.8)
BASFI	–	–	20.8 (8.2–45.5)	–	–	22.3 (8.9–41.5)
ASDAS	–	–	1.8 (1.1–2.8)	–	–	1.5 (0.9–2.3)
Physician global VAS, mm	6 (2–13)	6 (2–11)	5 (2–8)	5 (2–9)	3 (1–11)	3 (1–11)
Patient pain VAS, mm	27 (12–54)	31 (9–57)	22 (8–50)	19 (8–38)	24 (9–45)	20 (7–36)
Patient fatigue VAS, mm	44 (22–68)	52 (19–76)	45 (18–70)	28 (12–58)	31 (17–59)	29 (11–52)
Patient global VAS, mm	36 (13–60)	37 (17–68)	27 (10–55)	21 (8–49)	22 (10–46)	23 (8–42)
HAQ	0.6 (0.1–1.1)	0.8 (0.1–1.1)	0.4 (0.0–0.8)	0.5 (0.1–1.1)	0.4 (0.0–1.0)	0.3 (0–0.6)
PASS yes, n (%)	270 (56)	130 (53)	267 (60)	138 (68)	48 (69)	104 (65)
Comorbidities§						
Cancer, n (%)	10 (2)	7 (3)	6 (1)	5 (2)	<5	<5
Hospitalised infection, n (%)	132 (28)	58 (24)	80 (18)	64 (32)	19 (27)	36 (22)

Continued

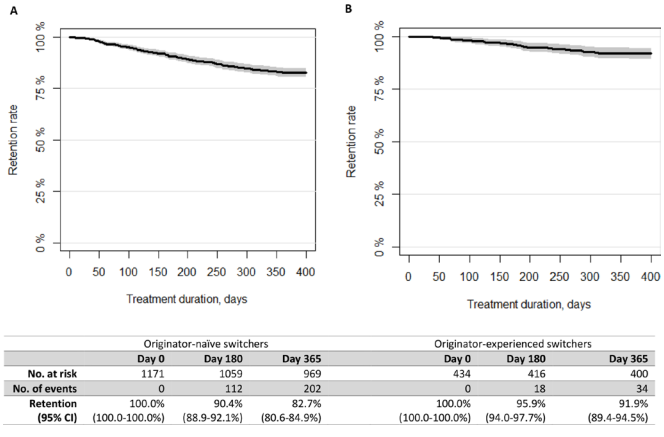
Table 1 Continued

	Originator-naïve switchers, N=**1171**			**Originator-experienced switchers, N=434**		
	RA*	**PsA**	**AxSpA**	**RA***	**PsA**	**AxSpA**
Knee/hip prosthesis, n (%)	50 (11)	11 (5)	11 (3)	21 (10)	<5	6 (4)
Pulmonary disease, n (%)	28 (6)	16 (7)	14 (3)	16 (8)	<5	1 (0.5)
Diabetes, n (%)	26 (5)	15 (6)	9 (2)	14 (7)	6 (9)	11 (7)
Myocardial infarction, n (%)	10 (2)	<5	<5	7 (3)	<5	5 (3)
Chronic kidney disease, n (%)	9 (2)	<5	<5	<5	<5	<5

Numbers are median (IQRs) unless otherwise stated. Baseline is time window from 90 days before to 6 days after switch date (baseline). Patient pain (VAS 0–100), fatigue (VAS 0–100), patient global assessment (VAS 0–100) and physician global VAS 0–100. For patient discretion, numbers below 5 are not presented.
*Also includes 55 patients with Juvenile RA, polyarthritis, reactive arthritis and other arthritis.
†DAS28/ASDAS remission defined as DAS28 <2.6 (RA and PsA), ASDAS <1.3 (AxSpA).
‡CDAI remission defined as <2.9 (RA and PsA).
§0–10 years prior to baseline and ever for cancer.
ASDAS, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis ; BASDAI, Bath Ankylosing Spondylitis (BAS) Disease Activity Index; BASFI, BAS Functional Index; bDMARD, biologic disease-modifying anti-rheumatic drug; BMI, body mass index; CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; MTX, methotrexate; PASS, Patient Acceptable Symptom State; PsA, psoriatic arthritis ; RA, rheumatoid arthritis ; VAS, Visual Analogue Scale.

Clinical characteristics are presented as medians (ranges) or numbers (percentages), as appropriate. GP1111 treatment retention was explored with Kaplan-Meier curves.

Baseline factors associated with retention were explored with univariable and multivariable Cox regression analyses. These were conducted for both subgroups combined (ie, all patients who switched from CT-P13 to GP1111) with previous originator treatment history included as a covariate. Analyses were performed as crude, age-adjusted and gender-adjusted, fully adjusted and further stratified by indication. For fully adjusted analyses, the following a priori defined variables were included based on literature review[14 19 20]: age, gender, originator treatment history (yes/no), concomitant methotrexate (yes/no), C-reactive protein (CRP), patient global score on a Visual Analogue Scale (VAS) and number of comorbidities ≥1 (yes/no).



	Originator-naïve switchers			Originator-experienced switchers		
	Day 0	Day 180	Day 365	Day 0	Day 180	Day 365
No. at risk	1171	1059	969	434	416	400
No. of events	0	112	202	0	18	34
Retention (95% CI)	100.0% (100.0-100.0%)	90.4% (88.9-92.1%)	82.7% (80.6-84.9%)	100.0% (100.0-100.0%)	95.9% (94.0-97.7%)	91.9% (89.4-94.5%)

Figure 2 Kaplan-Meier plots of crude treatment retention rates in GP1111-treated patients ((A) originator-naïve and (B) originator-experienced switchers)*.*The grey shaded area on the figures represents the 95% CI.

Disease activity in individual patients was assessed 4 months before baseline, at baseline and 4 months after baseline and changes preswitch and postswitch were calculated and compared using a paired t-test. If a patient had no registration of disease activity, data was registered

Table 2 Reasons for GP1111 withdrawal during 1-year follow-up

Reason, n (% of withdrawals)	Originator-naïve switchers n=**1171**	**Originator-experienced n=434**
Lack of effect	121 (60)	10 (29)
Adverse events	32 (16)	8 (23)
Cancer	0 (0)	<5
Remission	7 (3.5)	<5
Pregnancy	0 (0)	0 (0)
Infection	<5	0 (0)
Death	<5	<5
Lost to follow-up	<5	0 (0)
Moved to other hospital	6 (3)	<5
Surgery	0 (0)	0 (0)
Other	18 (9)	<5
Several reasons	6 (3)	<5
Unknown	6 (3)	<5
Total, n (%)	202 (100)	35 (100)

Reasons for withdrawal are reported according to the prespecified categories in DANBIO. For patient discretion, numbers below 5 are not presented.

Table 3 Baseline variables associated with GP1111 treatment withdrawal, performed in all switch patients (n=1605) and stratified by diagnosis

	Univariate		Age-adjusted and gender-adjusted		Fully adjusted*	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Rheumatoid arthritis, n=685						
Female gender	0.85 (0.58 to 1.26)	0.42	–		0.74 (0.48 to 1.14)	0.17
Age, years	1.00 (0.99 to 1.01)	0.92	–		1.01 (0.99 to 1.02)	0.50
Previous originator infliximab experienced (yes)	**0.48 (0.29 to 0.77)**	**0.002**	**0.46 (0.28 to 0.76)**	**0.002**	**0.36 (0.19 to 0.68)**	**0.001**
Methotrexate use, yes	**0.46 (0.31 to 0.67)**	**<0.001**	**0.45 (0.31 to 0.66)**	**<0.001**	**0.60 (0.39 to 0.93)**	**0.02**
Comorbidities ≥1	1.06 (0.73 to 1.54)	0.75	1.05 (0.73 to 1.53)	0.78	0.92 (0.60 to 1.42)	0.71
CRP, mg/L	**1.01 (1.00 to 1.02)**	**0.01**	**1.01 (1.00 to 1.02)**	**0.01**	1.00 (0.99 to 1.01)	0.59
Patient global VAS, mm	**1.02 (1.01 to 1.03)**	**<0.001**	**1.02 (1.01 to 1.03)**	**<0.001**	**1.02 (1.01 to 1.02)**	**<0.001**
In DAS28 remission (yes)	**0.38 (0.25 to 0.58)**	**<0.001**	**0.36 (0.24 to 0.56)**	**<0.001**	–	–
In CDAI remission (yes)	0.78 (0.51 to 1.19)	0.24	0.78 (0.51 to 1.19)	0.25	–	–
DAS28	**1.67 (1.43 to 1.95)**	**<0.001**	**1.70 (1.45 to 1.98)**	**<0.001**	–	–
CDAI	**1.06 (1.04 to 1.09)**	**<0.001**	**1.07 (1.04 to 1.09)**	**<0.001**	–	–
Psoriatic arthritis, n=314						
Female gender	0.88 (0.51 to 1.51)	0.64	–	–	0.71 (0.39 to 1.31)	0.28
Age, years	1.01 (0.99 to 1.03)	0.42	–	–	1.01 (0.99 to 1.04)	0.40
Previous originator infliximab experienced (yes)	**0.19 (0.06 to 0.62)**	**0.006**	**0.17 (0.05 to 0.54)**	**0.002**	**0.23 (0.07 to 0.75)**	**0.01**
Methotrexate use, yes	1.27 (0.72 to 2.23)	0.40	1.22 (0.68 to 2.18)	0.51	1.27 (0.66 to 2.44)	0.46
Comorbidities ≥1	1.52 (0.88 to 2.62)	0.14	1.53 (0.87 to 2.68)	0.14	1.06 (0.56 to 1.99)	0.86
CRP, mg/L	1.01 (1.00 to 1.03)	0.08	1.02 (1.00 to 1.03)	0.08	1.01 (0.99 to 1.03)	0.40
Patient global VAS, mm	**1.02 (1.01 to 1.03)**	**<0.001**	**1.02 (1.01 to 1.03)**	**<0.001**	**1.02 (1.00 to 1.03)**	**0.004**
In DAS28 remission (yes)	**0.40 (0.22 to 0.74)**	**0.003**	**0.37 (0.20 to 0.68)**	**0.001**	–	–
In CDAI remission (yes)	1.03 (0.55 to 1.92)	0.93	1.06 (0.56 to 2.01)	0.86	–	–
DAS28	**1.64 (1.27 to 2.13)**	**<0.001**	1.72 (1.31 to 2.25)	**<0.001**	–	–
CDAI	**1.08 (1.04 to 1.13)**	**<0.001**	**1.09 (1.05 to 1.14)**	**<0.001**	–	–
Axial spondyloarthritis, n=606						
Female gender	**1.66 (1.04 to 2.65)**	**0.04**	–	–	1.21 (0.71 to 2.05)	0.48
Age, years	1.00 (0.98 to 1.01)	0.64	–	–	1.00 (0.98 to 1.02)	0.98
Previous originator infliximab experienced (yes)	0.55 (0.29 to 1.02	0.06	0.59 (0.31 to 1.12)	0.10	0.60 (0.29 to 1.23)	0.16
Methotrexate use, yes	0.65 (0.30 to 1.42)	0.28	0.63 (0.29 to 1.39)	0.25	0.66 (0.29 to 1.46)	0.30
Comorbidities ≥1	1.10 (0.65 to 1.84)	0.72	1.11 (0.66 to 1.87)	0.69	0.95 (0.54 to 1.69)	0.86
CRP, mg/L	1.01 (0.99 to 1.04)	0.31	1.01 (0.99 to 1.04)	0.23	1.02 (0.99 to 1.05)	0.28
Patient global VAS, mm	**1.02 (1.01 to 1.02)**	**<0.001**	**1.01 (1.01 to 1.02)**	**<0.001**	**1.01 (1.01 to 1.02)**	**0.001**
In ASDAS remission (yes)	**0.41 (0.22 to 0.77)**	**0.005**	**0.42 (0.22 to 0.81)**	**0.008**	–	–
ASDAS	**1.50 (1.20 to 1.87)**	**<0.001**	**1.48 (1.18 to 1.85)**	**<0.001**	–	–

Bold values are those that were found to be significantly associated.
*Number of patients contributing to the analysis: rheumatoid arthritis: 571 (83%), psoriatic arthritis: 265 (84%), axial spondyloarthritis: 518 (85%).
ASDAS, Ankylosing Spondylitis Disease Activity Score; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; VAS, Visual Analogue Scale .

as missing. It was not considered meaningful to impute missing data on disease activity due to the fluctuating course of rheumatic diseases.

RESULTS

In total, 1605 patients performed an infliximab B2B-switch and were included; 1171 originator-naïve and 434 originator-experienced (table 1, online supplemental tables S2 and S3). At baseline, median disease duration was 9 years and 29–42% were in Clinical Disease Activity Index (CDAI) or Ankylosing Spondylitis Disease Activity Score remission.

Originator-naïve patients were younger, had shorter disease duration and fewer comorbidities than those

who were originator-experienced. Furthermore, baseline subjective and objective disease markers (eg, CRP, CDAI, patient global VAS) were higher, and fewer were in remission. Patients in both subgroups had median three visits during follow-up (table 1).

At 1 year, 83% (95% CI: 81% to 85%) of the originator-naïve and 92% (95% CI: 90% to 95%) of the originator-experienced switchers maintained GP1111 treatment (figure 2). Stratified by indication, the retention rate was 80–87% for originator-naïve (highest in AxSpA) and 90–96% for originator-experienced switchers (lowest in RA) (online supplemental figure S1).

Main reasons for withdrawal were lack of effect (originator naïve 60% and experienced 29%) and adverse events (16% and 23%) (table 2).

Risk of GP1111 withdrawal was lower in originator-experienced compared with naïve patients, mainly in patients with RA (HR=0.36, 95% CI: 0.19 to 0.68) and PsA (HR=0.23, 95% CI: 0.07 to 0.75), respectively. For all indications, higher baseline disease activity was associated with higher withdrawal (table 3).

For both originator-naïve and originator-experienced switchers, changes in disease activity preswitch and postswitch in individual patients were close to zero for all measures with no statistically significant differences (table 4).

DISCUSSION

In this nationwide cohort study among more than 1600 B2B-switch patients, we found high GP1111 treatment retention rates, with 8 of 10 originator-naïve switchers and 9 of 10 originator-experienced switchers maintaining treatment after 1 year. Similar rates have been reported in RCTs and observational studies for infliximab originator and biosimilar CT-P13.[5 6 14 27] Furthermore, we demonstrated stable disease activity before and after switching.

Biosimilar use and switch procedures vary across countries.[28–31] In some countries biosimilars are hardly used—potentially with huge impact on drug expenditures and access to treatment.[32] In Denmark, biosimilars are implemented at the time of marketing based on national tenders. The bDMARDs are provided free of charge to all patients via a tax-based system, and mandated switch procedures are implemented according to national guidelines.[14 19 20]

The European Medical Agency's approval of the biosimilar GP1111 was based on a phase III trial in previously infliximab-naïve patients with RA randomised to either GP111 or originator infliximab.[8 33] The extrapolation of this approval to also cover PsA, AxSpA, IBD and psoriasis could be challenged by factors differing across indications (age, genetics, drug dose, comorbidities, co-medications) potentially affecting immunogenicity, pharmacokinetics and/or dynamics.[2 34] Furthermore, the highly selected patients included in RCTs are not representative of patients in routine care, who are older and have more comorbidities or other complicating characteristics.[35]

Current evidence regarding B2B-switching is very limited. To date, no RCT or observational study has investigated infliximab B2B-switches in patients with inflammatory rheumatic disease. In a small IBD cohort (n=176) 1 year treatment retention rates for originator-experienced and originator-naïve were similar (85% vs 87%).[12] Unchanged retention and disease activity following infliximab B2B-switching have also been reported in other small observational studies among patients with IBD (n between 87 and 271) and psoriasis (n=96).[36–39] Well-conducted observational studies based on prospective data collection in well established registries in countries performing nationwide systematic switches can provide important evidence and may challenge the need for systematic clinical studies.[18 40]

Our study provides important knowledge regarding real-life effectiveness for different switch scenarios among patients with inflammatory arthritis. The originator-experienced patients had been treated with infliximab for many years and had lower disease activity. Both previous originator treatment history and lower disease activity at the time of switch, especially subjective markers (eg, patient global VAS), were associated with higher retention. This suggests treatment outcomes to be more affected by patient-related than drug-related factors and indicates the presence of a 'nocebo-effect', that is, negative expectations towards the drug.[17 33] Similar findings have been reported for originator to biosimilar infliximab switching.[2 14] The proportion of patients who discontinued treatment due to adverse events was similar to those previously reported in other real-world studies of biosimilar infliximab.[14 29–31] Details regarding type of adverse event could not be explored due to lacking data in DANBIO.

The Danish nationwide strategy of frequent mandatory biosimilar switches combined with routine-care prospective follow-up in DANBIO contributed a large cohort with high data completeness. Limitations include the reporting of associations and not definitive causal relationships due to the observational study design. Despite adjustment for several baseline variables, residual confounding cannot be excluded.

In conclusion, infliximab B2B-switching, both in originator-naïve and originator-experienced patients with inflammatory arthritis, was effective and safe. Retention to GP1111 was higher in originator-experienced switchers and patients in remission at the time of the switch, suggesting outcomes to be more affected by patient-related than drug-related factors.

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Table 4 Disease activity and functional status 4 months prior to GP1111 switch, at the time of switch and 4 months after switch, stratified by indication and by originator treatment history

	Originator-experienced switchers					Originator-naïve switchers				
	4 months preswitch	Switch (baseline)	4 months postswitch	Preswitch (delta values)*	Postswitch (delta values)*	4 months preswitch	Switch (baseline)	4 months postswitch	Preswitch (delta values)*	Postswitch (delta values)*
Rheumatoid arthritis n=203						**Rheumatoid arthritis n=482**				
DAS28	1.9 (1.5 to 2.4)	1.9 (1.4 to 2.5)	1.9 (1.5 to 2.5)	–0.04 (–0.3 to 0.5)	0.02 (–0.2 to 0.3)	2.4 (1.7 to 3.3)	2.4 (1.8 to 3.3)	2.2 (1.7 to 3.1)	0.02 (–0.7 to 0.7)	–0.2 (–0.8 to 0.3)
HAQ (0–3)	0.5 (0.1 to 1.0)	0.5 (0.1 to 1.1)	0.6 (0.1 to 1.3)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.6 (0.2 to 1.1)	0.6 (0.1 to 1.1)	0.6 (0.1 to 1.1)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)
CRP, mg/L	2.0 (1.0 to 4.2)	2.0 (0.9 to 3.6)	2.1 (1.0 to –5.0)	0.0 (–1.0 to 1.8)	0.1 (–0.3 to 1.0)	3.0 (1.1 to 7.0)	3.0 (1.1 to 6.9)	3.0 (1.7 to 6.1)	0.0 (–1.2 to 2.0)	0.0 (–2.5 to 1.4)
CDAI	3.5 (1.8 to 6.3)	2.9 (1.4 to 5.9)	3.2 (1.4 to 6.9)	0.2 (–0.8 to 1.0)	–0.3 (–1.1 to 0.6)	5.7 (2.3 to 10.8)	5.9 (2.4 to 10.4)	5.0 (2.0 to 9.5)	–0.6 (–3.6 to 3.4)	–0.4 (–3.9 to 1.7)
VAS patient global, mm	21 (11 to 51)	21 (8 to 49)	23 (8 to 51)	–1 (–6 to 3)	0 (–4 to 5)	34 (13 to 63)	37 (13 to 60)	32 (13 to 65)	0 (–11 to 9)	–1 (–13 to 8)
VAS pain, mm	20 (9 to 36)	19 (7 to 41)	23 (7 to 45)	–1 (–6 to 2)	1 (–4 to 6)	30 (12 to 54)	28 (12 to 55)	29 (11 to 56)	–1 (–9 to 7)	–1 (–11 to 6)
VAS fatigue, mm	28 (13 to 62)	28 (13 to 57)	32 (12 to 61)	0 (–4 to 5)	0 (–6 to 7)	46 (21 to 67)	44 (21 to 68)	46 (22 to 72)	0 (–9 to 9)	–1 (–12 to 9)
Psoriatic arthritis n=70						**Psoriatic arthritis n=244**				
DAS28	1.9 (1.6 to 2.5)	2.1 (1.6 to 2.4)	1.9 (1.5 to 2.5)	0.11 (–0.1 to 0.3)	–0.06 (–0.3 to 0.2)	2.1 (1.7 to 2.8)	2.1 (1.7 to 2.9)	2.3 (1.7 to 3.0)	–0.0 (–0.4 to 0.5)	0.01 (–0.4 to 0.3)
HAQ (0–3)	0.5 (0.0 to 0.9)	0.4 (0.0 to –1.0)	0.4 (0.0 to 0.9)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.8 (0.3 to 1.0)	0.8 (0.1 to 1.1)	0.8 (0.1 to 1.3)	0.0 (–0.1 to 0.1)	0.0 (–0.1 to 0.1)
CRP, mg/L	2.5 (0.9 to 4.2)	2.5 (1.0 to 3.6)	2.8 (1.0 to 4.2)	0.0 (–0.9 to 2.1)	0.0 (–1.3 to 0.0)	2.0 (1.0 to 4.1)	2.0 (1.0 to 4.0)	3.0 (1.0 to 4.0)	0.2 (–0.6 to 1.6)	0 (–1 to 2)
CDAI	2.9 (1.3 to 6.7)	3.8 (1.9 to 8.4)	3.3 (0.5 to 6.2)	0.1 (–0.6 to 2.1)	–0.3 (–1.1 to 1.3)	5.3 (2.3 to 8.9)	5.3 (2.0 to 10.0)	5.4 (2.5 to 10.0)	–0.3 (–2.0 to 2.3)	0.0 (–2.3 to 2.3)
VAS patient global, mm	21 (10 to 49)	22 (10 to 42)	21 (3 to 55)	0 (–4 to 5)	0 (–4 to 4)	37 (15 to 67)	38 (17 to 69)	38 (18 to 73)	–1 (–7 to 14)	1 (–9 to 9)
VAS pain, mm	17 (5 to 45)	25 (5 to 38)	14 (3 to 46)	0 (–4 to 4)	0 (–4 to 5)	29 (14 to 60)	32 (9 to 60)	32 (14 to 63)	0 (–8 to 9)	1 (–9 to 9)
VAS fatigue, mm	34 (8 to 65)	31 (12 to 57)	36 (9 to 59)	–3 (–9 to 1)	4 (–0.3 to 11)	53 (24 to 75)	53 (17 to 76)	57 (29 to 80)	–1 (–9 to 10)	3 (–4 to 13)
Axial spondyloarthritis n=161						**Axial spondyloarthritis n=445**				
BASDAI, mm	21 (6 to 33)	21 (7 to 36)	24 (9 to 39)	–0 (–6 to 5)	0.0 (–5 to 4)	29 (14 to 48)	28 (12 to 53)	27 (11 to 52)	0 (–6 to 7)	–1 (–9 to 6)
ASDAS	1.5 (0.9 to 2.2)	1.5 (0.9 to 2.3)	1.6 (1.1 to 2.4)	–0.1 (–0.4 to 0.3)	0.1 (–0.2 to 0.3)	1.8 (1.0 to 2.7)	1.8 (1.1 to 2.8)	1.7 (1.1 to 2.8)	0.0 (–0.3 to 0.5)	–0.02 (–0.4 to 0.4)
CRP, mg/L	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	2.5 (1.0 to 4.8)	0.0 (–0.8 to 0.4)	0.1 (0.0 to 1.3)	2.0 (1.0 to 4.0)	2.7 (1.0 to 4.0)	3.0 (1.0 to 4.0)	0.0 (–0.5 to 2.0)	0.0 (–0.9 to 1.0)
VAS patient global, mm	20 (7 to 42)	22 (10 to 40)	22 (8 to 59)	–1 (–8 to 3)	0 (–4 to 8)	31 (12 to 58)	27 (10 to 54)	29 (9 to 59)	0 (–11 to 8)	0 (–9 to 8)
VAS pain, mm	20 (5 to 37)	19 (7 to 33)	21 (4 to 41)	–1 (–9 to 3)	0 (–3 to 6)	26 (9 to 50)	23 (8 to 50)	23 (8 to 49)	–1 (–9 to 8)	–1 (–10 to 7)

Continued

Table 4 Continued

	Originator-experienced switchers					Originator-naïve switchers				
	4 months preswitch	Switch (baseline)	4 months postswitch	Preswitch (delta values)*	Postswitch (delta values)*	4 months preswitch	Switch (baseline)	4 months postswitch	Preswitch (delta values)*	Postswitch (delta values)*
VAS fatigue, mm	27 (11 to 58)	27 (11 to 47)	29 (13 to 58)	−2 (−6 to 4)	−1 (−4 to 7)	45 (19 to 71)	43 (18 to 70)	43 (16 to 68)	0 (−11 to 11)	−1 (−12 to 6)

Numbers are medians (IQRs) unless otherwise stated.
Time windows preswitch: 4 months' window: −180 days to −91 days before start of GP1111, time windows switch: −90 days to +6 days after start of GP1111, time window postswitch: 4 months' window: +7 days to +180 days after start of GP1111. In case of several visits within a given time window, the visit closest to the given time point was selected If a patient had no registrations, data will be registered as missing for that visit. For patients who withdrew <6 months postswitch, data from latest registered visit after baseline was carried forward. Patient pain (VAS 0–100), fatigue (VAS 0–100), patient global assessment (VAS 0–100).
*Delta values are changes in disease activity at time of switch minus 4 months before switch (preswitch), and 4 months after switch minus at the time of switch (postswitch) in individual patients. Paired t-tests were performed to compare changes in disease activity (delta values) preswitch and postswitch and showed no statistically significant differences (all p values>0.05).
ASDAS, Ankylosing Spondylitis Disease Activity Score; AxSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis (BAS) Disease Activity Index; BASFI, BAS Functional Index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; HAQ, Health assessment Questionnaire; VAS, Visual Analogue Scale .

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