

## ORIGINAL ARTICLE

# 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

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## ABSTRACT

**Objectives** National Danish guidelines in May 2015 dictated a mandatory switch from originator infliximab (INX) to biosimilar CT-P13 in patients with inflammatory rheumatic disease. We investigated if this non-medical switch changed use of outpatient hospital resources.

**Methods** Observational cohort study. Switchers were identified in DANBIO. Rheumatic outpatient contacts, visits and services were identified in the National Patient Registry. The 6-month rate for (1) number of visits (or services) and (2) days with  $\geq 1$  visit (or service) were compared before/after switching (paired t-tests). Visits per week per patient before/after the switch date were analysed with graphical interrupted time-series analysis.

**Results** In 769 switchers (372 males, median age 54 years (IQR 44–66)), 1484 outpatient contacts, 6718 visits and 9243 days with services (693 on switch date) were identified. Mean visit rate was 3.89 before and 3.95 after switch ( $p=0.35$ ). Total number of services was 19 752 (2019 on switch date). Mean rates before/after switch for 16 service categories were small and differences close to zero. Visits per week per patient appeared similar before/after switch with peaks every  $\approx 8$  weeks (standard INX infusion interval).

**Conclusion** Changes were marginal with no clinically relevant increase in use of outpatient health care resources 6 months after compared with 6 months before mandatory switch from originator to biosimilar infliximab.

Availability of the cheaper biosimilar disease-modifying antirheumatic drugs (bsDMARDs) has raised financial incentives to change treatment practice.<sup>1,2</sup> Recent European League Against Rheumatism guidelines state that biosimilars should be included in treatment algorithms on equal terms as the originator.<sup>3</sup> However, recommendations are debated regarding non-medical switching (ie, switching for economic

## Key messages

### What is already known about this subject?

- Switching from originator to cheaper biosimilar biological agents has been suggested for economic reasons among patients with inflammatory arthritis.
- Existing literature provides no data about the cost consequences of such non-medical switching.

### What does this study add?

- We found no evidence of changes in use of outpatient health resources following switch from originator to biosimilar infliximab.

### How might this impact on clinical practice?

- This study demonstrated no immediate cost consequences of non-medical switching in routine care.

reasons in patients on stable treatment with the originator).<sup>4–6</sup>

In May 2015, Danish nationwide guidelines dictated a mandatory switch from originator (Remicade, INX) to biosimilar infliximab (Remsima, CT-P13) since the cost of CT-P13 was 36% of INX.<sup>7</sup> Non-medical switching might potentially induce uncertainty for patients and lead to an increased number of contacts to the healthcare provider for patient education or closer monitoring of the disease.<sup>8–10</sup> This could impose additional costs on healthcare services potentially off-setting savings from the cheaper product. Existing evidence provides no meaningful data about the cost consequences of switching. Previous budget impact and pharmacoeconomic analyses in autoimmune diseases have mainly included drug costs and prescription patterns and disregarded the impact on use of healthcare services.<sup>2,11–13</sup>

The nationwide clinical DANBIO registry prospectively collates detailed clinical information among patients with inflammatory arthritis.<sup>14</sup> These data, combined with administrative national health registries, offer a unique opportunity to assess use of healthcare resources in relation to switching. Thus, we aimed to investigate if switching from INX to CT-P13 in patients with inflammatory arthritis affected outpatient consultation rates and services provided within departments of rheumatology 6 months after compared with 6 months before the switch.

## MATERIALS AND METHODS

### Study population

The study population was identified in DANBIO and included INX-treated patients (rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis) who switched from INX to CT-P13 between 20 March and 1 January 2016 (=switchers).<sup>7</sup> Treatment regimen and switch date were obtained from DANBIO. Switch date was validated by the local departments of rheumatology.<sup>7</sup> Vital status (=alive) by 1 August 2016 was confirmed through the central person register. Only patients alive during the full 6-month observation period were included.

The Danish National Patient Registry is virtually complete. It is organised with one record for each patient contact (which could be a series of visits for the same health problem).<sup>15</sup> Information on all hospital outpatient contacts (completed and ongoing) was obtained. Patients were included if they had  $\geq 1$  outpatient contact related to inflammatory joint disease at departments

that registered patients in DANBIO. In Denmark, infusions with biological DMARDs are administered at these departments.

Each outpatient contact consists of a number of outpatient visits (ie, physical visits) with corresponding visit dates and records of services provided. Services are coded by date and type of service. Only records for visits and services dated 0–6 months before and after the switch date were included in this analysis. Services were categorised into 16 meaningful groups of relevance to INX treatment for inflammatory rheumatic diseases (shown in table 1). All visits and services provided by physicians and nurses (but not secretaries) related to outpatient contacts were included in the analysis.

Analyses were performed in Stata V.15.1 (StataCorp). For individual switch patients, the following rates were calculated for the 6-month period before and after switch: (1) days with  $\geq 1$  outpatient visit and (2) number of visits. Similar calculations were done for outpatient services. Visits and services performed on the switch date were analysed separately.

Differences in rates before versus after switch were compared by paired t-tests.

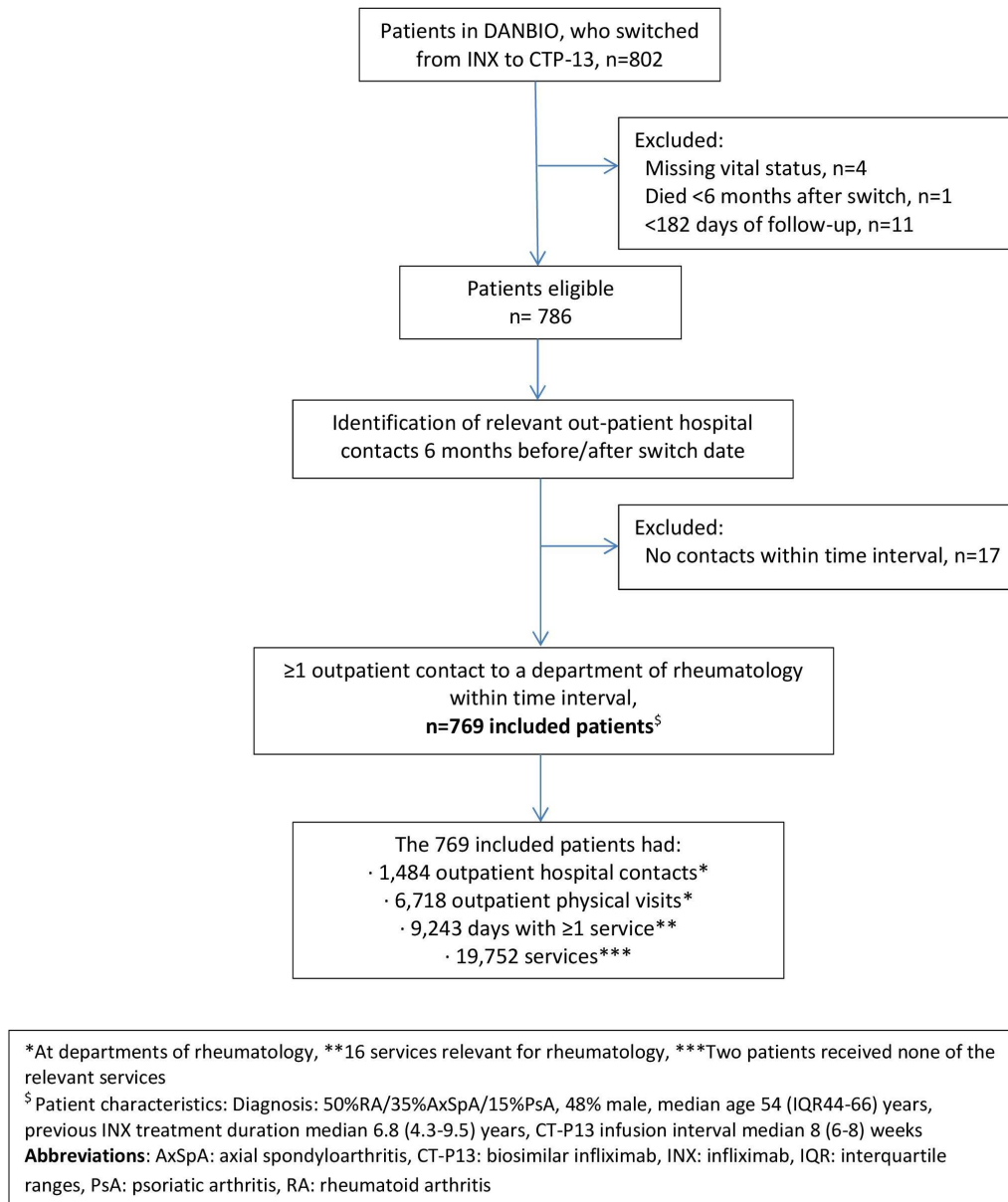
Switchers were also categorised according to change in number of services (fewer/the same/more) before versus after switch, and the service rates were compared for these categories.

The weekly rate of outpatient visits before and after the switch date was analysed with graphical interrupted time-series analysis.<sup>16</sup>

**Table 1** (A) Rate of services per patient 6 months before and after the switch, the difference and p values (paired t-test); (B) number of patients with no registered use of services; and (C) number of patients with changes in number of services

Service	A. Mean rate of services per patient				B. Non-users (% of all)	C. Patients with changes in number of services, n (% of patients who change)		
	Before	After	Difference	P level		Less	Unchanged	More
Outpatient visit	1.44	1.45	0.00	0.91	427 (56)	107 (31)	139 (41)	96 (28)
Nurse activity	0.61	0.58	-0.03	0.22	601 (78)	53 (32)	69 (41)	46 (27)
csDMARD	0.30	0.32	0.02	0.36	595 (77)	73 (42)	27 (16)	74 (43)
Intravenous needle	0.36	0.37	0.01	0.61	666 (87)	28 (27)	38 (37)	37 (36)
Infliximab treatment	3.10	2.96	-0.13	<0.01	11 (1)	229 (30)	330 (44)	199 (26)
Consultation regarding treatment	0.09	0.07	-0.02	0.12	723 (94)	24 (52)	5 (11)	17 (37)
Phone consultation	1.03	1.17	0.14	0.03	237 (31)	219 (41)	65 (12)	248 (47)
Patient guidance	0.35	0.49	0.14	<0.01	584 (76)	47 (25)	48 (26)	90 (49)
Intravenous medication	0.03	0.11	0.08	<0.01	697 (91)	16 (22)	2 (3)	54 (75)
Methotrexate	0.60	0.61	0.01	0.73	557 (72)	84 (40)	48 (23)	80 (38)
US shoulder, elbow, hand	0.09	0.07	-0.02	0.23	689 (90)	42 (53)	7 (9)	31 (39)
US hip, knee, foot	0.08	0.10	0.01	0.30	681 (90)	35 (40)	10 (11)	43 (49)
Clinical investigation	0.31	0.47	0.16	<0.01	552 (72)	53 (24)	63 (29)	101 (47)
Clinical control	2.08	2.26	0.19	<0.01	206 (27)	153 (27)	198 (35)	212 (38)
Observation	0.17	0.22	0.05	<0.01	714 (93)	7 (13)	22 (40)	26 (47)
BP measurement	0.61	0.60	-0.01	0.70	611 (79)	39 (25)	75 (47)	44 (28)

BP, blood pressure; csDMARD, conventional synthetic disease-modifying antirheumatic drug; US, ultrasound.



**Figure 1** Identification of switch patients and relevant hospital contacts. N, patient numbers.

## RESULTS

### Patient cohort and outpatient contacts

Among 802 switchers identified in DANBIO, 769 patients were included in the analysis (figure 1). In these patients, 5091 outpatient hospital contacts (completed and ongoing) were identified, whereof 1484 contacts were related to INX treatment at departments using DANBIO (figure 1). The 769 included patients had a total of 6718 visits that occurred within 6 months before (n=2995, 45%), on (689, 10%), or 6 months after (n=3034, 45%) the switch date. Overall, 19 752 services were provided (2019 of these were on the switch date).

### Days with visits 6 months before and after switch

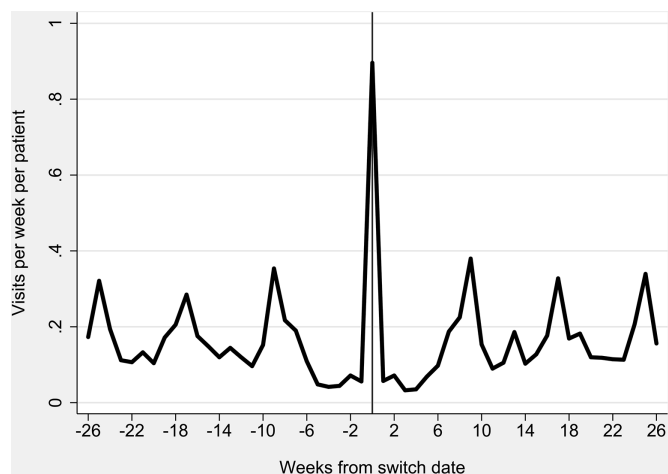
Mean visit rate was 3.89 before and 3.95 after switch (p=0.35). After the switch, 239 patients (31%) had fewer

(mean -1.6, SD 1.0), 271 patients (35%) had the same and 259 patients (34%) had more visits (mean 1.6, SD 1.0) than before switch.

The weekly rate of visits per patient appeared stable during the time period (figure 2). The peaks observed approximately every 8 weeks were consistent with clinical practice (standard INX infusion interval).

### Days with services

The total number of days with services were 4131 before (mean 5.4 days SD 2.8) and 4400 after switch (mean 5.8 days SD 2.8) (p<0.01, paired t-test). After the switch, 259 patients (34%) had fewer (mean -2.4, SD 1.7), 169 patients (22%) had the same and 341 patients (45%) (mean 2.6, SD 2.0) had more days with services than before switch.



**Figure 2** Weekly rates of physical visits per patient 6 months before and 6 months after switching.

### Analysis of services provided

The rates of provided services declined after switch for INX treatment and increased for telephone consultations, patient guidance, intravenous medication, clinical investigations and controls, and observations. Numerical differences were, however, small and close to zero (table 1).

The number of patients with changes in provided services before versus after switch (less/more) appeared similar (table 1)

### DISCUSSION

In this study of 769 patients with inflammatory arthritis who switched from INX to CT-P13 in routine care, we found only minor, clinically insignificant changes in the use of outpatient health resources during a 6-month time period after the switch compared with before the switch.

The biosimilars are expected to provide similar standard care at lower costs, thus facilitating better access to treatment and perhaps earlier treatment during the disease course, which has major potential social perspectives.<sup>4,8</sup> The availability of bsDMARDs has been reported to cause changes in prescription practice, although the uptake of bsDMARD varies markedly between countries.<sup>8</sup> Previous pharmaco-economic and budget impact analyses have mainly included direct costs of the medication.<sup>11,13</sup> To our knowledge, no previous studies have investigated the use of healthcare resources accompanying switching to bsDMARDs.

Discussions on how to use the cheaper biosimilar drugs in patients on stable treatment with the originator drug are ongoing.<sup>5,6</sup> According to the Danish guidelines, switching was mandatory and INX was no longer routinely available.<sup>17</sup> Within few months, CT-P13 acquired the majority of the INX market share across indications in Denmark.<sup>18</sup> We have previously reported 1-year effectiveness outcomes in the patient cohort.<sup>7</sup>

In the current study of the impact of non-medical switch on the use of healthcare resources, we used three

different indicators: physical visits, days with services and number of services provided. Neither gave indications of substantial changes after switching. The visit rate was unchanged, while the number of services increased slightly after the switch with a minor increase in telephone consultations and clinical investigations/controls. However, these services were only provided for a small proportion of the patients (7%–16%). Although the use of telephone consultations increased slightly, the associated activity-based fee (DRG-tariffs (18€))<sup>19</sup> is modest.

Previous studies have reported that patients and healthcare professionals often are somewhat reluctant to implement the use of bsDMARDs.<sup>9</sup> Negative expectations (=nocebo effects) are suspected to have an impact on treatment effects and costs.<sup>10,20,21</sup> It is reassuring that we found only minor changes in the use of healthcare resources, despite the switch being mandatory and that no specific strategy for patient information was set up. The fact that patients were informed about the switch at an already scheduled appointment could potentially reduce the nocebo effect—treatment was handled ‘as usual’. Some patients may not have been aware of the switch, but this cannot be explored with the available data.

This study has strengths and limitations. The availability of valid and virtually complete data from routine clinical and administrative national registries was a strength. The validity of diagnoses and treatments in DANBIO is high.<sup>22</sup> The switch date in DANBIO coincided with a physical visit for the vast majority of patients, only ≈10% of patients had no physical visit (figure 2) or service provided on that date. This might be due to imprecise registration in DANBIO or errors in data coding. The registration of physical visits and days with services in the national patient registry has high validity.<sup>15</sup> Although there seemed to be some variation in the routines regarding registration of services between departments, the paired analyses were robust to such variation. The service rate during the 6-month period following switch seemed stable, which indicates that the time period that was chosen for the investigation of a potential impact of the switch was relevant. However, we have no information regarding the duration of the individual services provided; thus, if the switch induced longer and more elaborate consultations/phone calls, this has not been captured.

In conclusion, this study does not provide evidence of an increased use of outpatient healthcare resources in departments of rheumatology following the nationwide mandatory switch from originator to biosimilar INX.

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