Uptake of rheumatology biosimilars in the absence of forced switching

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Abstract

Background: To describe the uptake and system-level effects of the introduction of biosimilars in a setting without forced switching.

Research design and methods: We used data from the Swedish Rheumatology Quality register from start of marketing of infliximab (Remsima® and Inflectra®) and etanercept (Benepali®) biosimilars until December 31st 2016. We compared users of each originator-product and its biosimilar(s) by line of treatment: bDMARD-naïve patients, non-medical switchers (vs. matched patients remaining on originator), and patients switching from a previous bDMARD of another type.

Results: From start of marketing (March 1st 2015) and December 31th 2016 (22 months) 1343 patients started an infliximab biosimilar. For etanercept (April 1st through December 31th 2016 (9 months), the corresponding number was 2691 patients. Overall, the introduction of these biosimilars resulted in an increase of the total number of ongoing infliximab and etanercept treatments (originator + biosimilar) during the study period. At the end of the study period, biosimilars accounted for 31% of all infliximab treatments and 31% of all etanercept-treated patients. For each line of therapy, we noted only small differences in patient characteristics between those starting the originator product vs. its biosimilar(s).

Conclusions: Introduction of biosimilars have effects beyond replacement of the originator product, in terms of an increased rate of bDMARD initiation. Selection to non-medical switching displayed no particular disease- or patient-characteristics.

Key words: bDMARDs, biosimilar

1. Introduction

Since 1999, a growing number of biological disease modifying anti-rheumatic drugs (bDMARD) have been approved. Because of their effectiveness and high costs, their use has markedly changed the treatment landscape in rheumatology and similar therapeutic areas.[1] Following patent expiration of several of the originator products, biosimilars have been introduced in clinical care. For regulatory approval, pharmacokinetics, pharmacodynamics and efficacy should be demonstrated to be comparable to the originator drug.[2] Because of the complex structure of bDMARDs, and the non-identical manufacturing processes for originator products and biosimilars, the market entry of biosimilars has been linked to concerns from patients and from their care-providers regarding their use in clinical practice. In particular, there is limited data on whether switching from an originator product to its biosimilar (the originator has reached its intended effect and the medical condition does not warrant replacement to a biosimilar, henceforth referred to as non-medical switch) can be made without loss of effectiveness or increased risk of adverse events.

Different countries have approached the introduction of biosimilars differently, in part reflecting the concerns above but mostly reflecting differences in tender and pricing policies, and in the individual prescribers' freedom in drug choice.[3, 4] Such differences may profoundly influence not only the uptake of biosimilars, but also the characteristics of patients selected for treatment with a biosimilar versus the originator product. Any such differences, in turn, are likely to affect the observed clinical effectiveness, drug survival, and safety.

In light of the uncertainty regarding the “real world similarity” of biosimilars, the aims of this study were to describe the uptake of infliximab and etanercept biosimilars for the treatment of rheumatic diseases in a setting without nation-wide forced switching, and to describe and compare the characteristics of patients starting a biosimilar or the originator product in this context.

2. Patients and Methods

2_1. Setting

Sweden is a Scandinavian country with 10 million inhabitants. The prevalence of rheumatoid arthritis (RA) in Sweden is around 0.7% [5, 6] while the combined prevalence of ankylosing spondylitis (AS), psoriatic arthritis (PsA) and other spondyloarthropathy (SpA) is around half that of RA. [7, 8]

Swedish health-care is tax-funded and offers universal access. Regional economical agreements for pricing has resulted in geographical differences in choice of first-line biologics. For drugs administered at healthcare units (e.g. infliximab) regional economical agreements for pricing and recommendation of preferred drugs exist in Sweden, while for drugs on prescription to pharmacies (e.g. etanercept) such agreements are not allowed.

In contrast to other countries in which switching from originator to biosimilar has been mandatory and forced, Swedish health authorities have not instituted any mandatory switching. Instead, the ultimate decision to treat with biologics (and, if so, with originator or biosimilar) resides with the treating physician. Guidelines by the Swedish Society for Rheumatology (SRF) initially issued a cautious approach to biosimilars, but once clinically available, switching from originator product to biosimilar has been endorsed for (informed) patients in stable remission or with a stable low disease activity. The Swedish Rheumatology Quality Register (SRQ) was started in 1995, and the estimated coverage for bDMARD-treated patients is 95% for RA and 86% for AS.[9]

2_2. Study population

By December 31st 2016, end of the study period, the Swedish Rheumatology Quality Register included information on 82,794 patients with rheumatic conditions. Among these, we included

all patients with RA, AS, PsA, or SpA who initiated an infliximab treatment (originator Remicade®, biosimilars Remsima® or Inflectra® (CT-P13)) after the time of biosimilar market entry in Sweden March 1st 2015. Similarly, we included all patients initiating etanercept (originator Enbrel®, biosimilar Benepali® (SB4)), after its market entry April 1st 2016. We also included all patients with RA, AS, PsA, or SpA who were *on treatment* with Remicade® by March 1st, 2015 and all patients who were *on treatment* with Enbrel by April 1st, 2016.

2_3. Patient characteristics

In SRQ, we identified information on age at start of treatment, gender, region of residence, disease characteristics, bDMARD treatment history, and vital status.

2_4. Statistical analysis

Differences between initiators of originators and biosimilars regarding demographics, previous treatment, and disease characteristics were tabulated using medians and percentages. Patients were stratified according to treatment (originator vs. biosimilar) and according to line of therapy: (i) bDMARD-naïve patients, (ii) patients switching from the originator to its biosimilar (non-medical switchers), and (iii) patients starting a biosimilar within six months after discontinuing (for any reason) a previous bDMARD of another type.

To assess differences between patients who started the originator vs. its biosimilar, we used multivariable linear regression, with bootstrapped 95% confidence intervals (CIs) to account for the skewed distribution of most outcomes. Models for age, gender, indication, and baseline disease characteristics were mutually adjusted, and additionally adjusted for geographical region.

For non-medical switchers, there was no readily available comparator group. Instead, we matched each patient in the non-medical switch group to five patients who, at the time of the index patient's switch, were still on the originator product. To allow identification of differences

between the originator and the biosimilar users, no other factors were considered for the matching.

3. Results

Between March 1st 2015 and December 31th 2016, 1865 patients started an infliximab treatment, of whom 522 started Remicade and 1343 started an infliximab biosimilar (1050 started Remsima, 293 started Inflectra). Between April 1st 2016, and December 31th 2016, 2940 patients started an etanercept treatment, of whom 249 started the originator Enbrel and 2691 started the biosimilar Benepali.

Figure 1 A and B shows the number of patients with *ongoing* infliximab and etanercept treatment over time. The number on infliximab was stable (~2900) before marketing of infliximab biosimilars, and reached 3080 patients at the end of the study period. The number of ongoing etanercept treatments was increasing before marketing of the biosimilar, and increased further thereafter. At the end of the study period (22 months after market entry of infliximab, and 9 months after market entry of etanercept biosimilars), biosimilars accounted for 31% of all infliximab treatments and 31% of all etanercept-treated patients.

The introduction of biosimilars was associated with an increase in the total number of patients on any bDMARD, in particular after the introduction of Benepali in April 2016 (Figure 1C). For the period January 2013 until March 2015 the number of patients currently on any bDMARD was increasing by on average 125 new patients per month, whereas the corresponding increase for April 2016 through January 2017 was 165 per month. Moreover, we observed a decrease in patients on bDMARDs other than infliximab or etanercept, from an increase of 103 patients per month in the period January 2013-March 2015, to an increase of 68 patients per month in the period April 2016-January 2017.

Among bDMARD-naïve patients starting infliximab or etanercept, and among patients who switched to a biosimilar from a bDMARD other than the originator product, multivariable adjusted models did not demonstrate any significant differences between those starting an originator vs. its biosimilar (Appendix Table A1 and A2). We did however observe regional differences, more pronounced for infliximab than for etanercept, with some clinics showing strong preferences for either the biosimilar or the originator product (Appendix Table A3).

For non-medical switchers, we detected no significant differences comparing biosimilar initiators to their matched originator-product references individuals, except that non-medical switches had a shorter time on originator product (only etanercept), higher CRP levels (only infliximab) and higher concomitant use of methotrexate (both infliximab and etanercept) and NSAIDs (only infliximab) (Table 1).

4. Discussion

This study describes the uptake and system-level effects of introducing biosimilars into a setting with no forced switch, Swedish Rheumatology. Our results suggest that the introduction of biosimilars not only replaced part of the market of their originator products, but also may have contributed to an increase in the overall use of bDMARDs. Despite clear price differences between originator and biosimilar, the uptake of the latter was moderate, yet faster for the second biosimilar introduced (etanercept) than for the first (infliximab). Besides regional pricing agreements for infliximab that may have negatively impacted the economic incentive to switch, discussions of increased immunogenicity for infliximab,[10] and being the first biosimilar on the market, might explain the slower rate of non-medical switch. Small, or no, differences were observed in disease characteristics between patients starting the originator or the biosimilar, after stratification by line of therapy.

This study has several strengths. The SRQ is a large register with high coverage [9] and extensive information on patient characteristics and disease history. In contrast to for instance

Denmark,[4] non-medical switch in Sweden has not been mandatory at the national level, thus allowing us to make comparisons between patients selected for originator or biosimilar treatment, both in the context of new-starters and in the context of non-medical switchers.

A limitation of this study was the assessment of disease characteristics; information was not always available at start of the treatment/switch. Therefore, we collected covariate information from the visit closest to the start of the treatment among all the visits that occurred between 90 days prior and 30 days after the prescription. However, for non-medical switchers and their comparators we retrieved information on disease characteristics at the last recorded visit ever, since the patients stable on drug are seen less often by the rheumatologist. The reported results cannot be generalized to other countries since we cannot assume that the strategy adopted by Sweden of a non-mandatory switch would have the same effects in other countries. A different purchasing systems of biopharmaceuticals and a different approach to the biosimilar by doctor and patients could lead to a completely different situation, in which the uptake of the biosimilars and the influence on the overall number of bDMARDs might differ.

5. Conclusions

In this first assessment of the uptake of biosimilars in Sweden, we observed effects beyond simple replacement of the originator product. Non-medical switch did not seem dependent on key disease- or treatment characteristics. It will now be an important task to assess whether co-morbidities, or contextual factors differ between originators and their biosimilars and how they affect drug survival and treatment outcomes.

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Figure 1. Number of *ongoing treatments* with infliximab (A), etanercept (B) and overall bDMARDs (C, TNFi and non-TNFi)* in Sweden by month, between January 1st 2014 and December 31st 2016, stratified by originator product and its biosimilar(s).

*Slope before March 2015: +125 pts/ Month ; slope after April 2016: +165 pts / Month

Table 1. Disease characteristics of non-medical switchers of infliximab between March 1st 2015 and December 31th 2016, or etanercept between 1 April 2016 and December 31th 2016 in Sweden, and a matched sample who did not switch. Mean differences of biosimilar vs. originator were estimated using multivariable linear regression models, adjusted for all other variables and region.

	<i>Infliximab</i>			<i>Etanercept</i>		
	Originator	Biosimilar	Mean difference*	Originator	Biosimilar	Mean difference*
N	2645	529		5845	1169	
<i>Age, years (mean, SD)</i>	56 (14)	57 (14)	0.7 (-0.4,1.7)	56 (14)	56 (14)	0.2 (-0.6,1.0)
<i>Gender (%)</i>	1391 (52.6)	256 (48.4)	1.2 (-4.4,6.9)	3717 (63.6)	754 (64.5)	0.4 (-2.6,3.3)
<i>Indication (%):</i>						
<i>RA</i>	52.1%	49.3%	0.3 (-4.0,4.6)	60.5%	63.0%	0.8 (-1.7,3.4)
<i>PsA</i>	17.2%	18.7%	0.0 (-4.8,4.8)	21.0%	21.5%	-0.1 (-3.0,2.8)
<i>SpA</i>	9.9%	13.0%	-0.8 (-5.0,3.4)	8.8%	8.0%	-0.3 (-1.9,1.3)
<i>AS</i>	20.7%	18.9%	0.5 (-3.2,4.1)	9.7%	7.6%	-0.4 (-1.9,1.1)
<i>Baseline characteristics[‡]:</i>						
<i>Disease duration, years (mean, SD)</i>	17.4 (11.7)	19.5 (10.7)	0.3 (-0.9,1.4)	17.6 (11.5)	16.8 (11.4)	-0.0 (-0.7,0.6)
<i>Time on originator, years (mean, SD)</i>	5.5 (4.5)	7.3 (4.5)	0.4 (-0.1,0.9)	5.6 (4.40)	5.0 (4.3)	-0.3 (-0.5,-0.1)
<i>HAQ, VAS scale (mean, SD)</i>	0.9 (0.6)	0.9 (0.6)	-0.0 (-0.1,0.0)	0.9 (0.6)	0.9 (0.6)	-0.0 (-0.1,0.0)
<i>ESR,mm/h (mean, SD)</i>	24 (22)	26 (23)	-1.6 (-3.5,0.3)	23 (20)	23 (20)	0.2 (-1.0,1.4)
<i>CRP,mg/dl (mean, SD)</i>	19 (27)	22 (32)	1.9 (0.2,3.6)	15 (21)	15 (23)	0.7 (-0.6,1.9)
<i>Pain\$,VAS scale (mean, SD)</i>	50 (27)	52 (25)	1.6 (-0.5,3.7)	50 (26)	50 (26)	0.1 (-1.4,1.6)
<i>Concomitant use of (%):</i>						
<i>MTX</i>	1851	359 (68.5)	4.5 (0.0,8.9)	3040	675 (58.4)	4.8 (1.9,7.7)

	(72.1)			(52.8)		
<i>Non-MTX csDMARDs</i>	398 (15.5)	94 (17.9)	3.0 (-0.6,6.7)	803 (14.0)	167 (14.5)	0.2 (-2.4,2.8)
<i>Oral corticosteroids (%)</i>	779 (30.3)	177 (33.8)	-2.3 (-8.1,3.5)	1963	410 (35.5)	-0.1 (-2.8,2.6)
				(34.1)		
<i>NSAIDs (%)</i>	1111	278 (53.1)	4.4 (0.4,8.4)	2325	448 (38.8)	2.8 (-0.6,6.1)
	(43.3)			(40.4)		

Abbreviations: HAQ = Health Assessment Questionnaire Disability Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; MTX = methotrexate, DMARDs = disease-modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drug.

§ Pain was measured on the Visual analogue scale (VAS)

[±] Information on baseline characteristics is collected from the last visit before the index date (date of switching to biosimilar for the case and for the matched controls)

*Mean differences are mutually adjusted, and additionally adjusted for region.

ICD-10 codes used for the analysis:

RA = M05.3, M05.8, M05.9, M06.0, M06.4, M06.8, M06.9, M08.0, M12.3, M13.0

PsA = ICD-10 codes: M07.0 + L40.5, M07.1 + L40.5, M07.2 + L40.5, M07.3x + L40.5

SpA = ICD-10 codes: M07.4, M07.5, M08.1, M46.1, M46.8, M46.9

AS = ICD-10 codes: M45.9

Table A1: Disease characteristics of bDMARD-naïve patients with RA, AS, SpA or PsA starting infliximab as first ever biologic between March 1st 2015 and December 31th 2016, or etanercept as first ever biologic between 1 April 2016 and December 31th 2016 in Sweden. Mean differences of biosimilar vs. originator were estimated using multivariable linear regression models, adjusted for all other variables in table, and region of residency.

	<i>Infliximab</i>			<i>Etanercept</i>		
	Originator	Biosimilar	Mean difference*	Originator	Biosimilar	Mean difference*
N	339	526		95	933	
<i>Age, years (mean, SD)</i>	52 (16)	51 (16)	-1.4 (-3.2,0.5)	53 (15)	50 (15)	-1.2 (-3.8,1.4)
<i>Gender (%)</i>	194 (57.2)	318 (60.5)		63 (66.3)	594 (63.7)	-4.2 (-14.5,6.2)
			0.1 (-7.7,7.9)			
<i>Indication (%):</i>						
<i>RA</i>	47.5%	46.8%	-0.3 (-6.8,6.1)	57.9%	53.8%	-1.0 (-9.2,7.3)
<i>PsA</i>	20.9%	23.8%	1.2 (-4.7,7.0)	23.2%	22.6%	-0.2 (-9.5,9.0)
<i>SpA</i>	14.7%	15.6%	0.8 (-4.7,6.3)	11.6%	14.4%	0.4 (-6.5,7.3)
<i>AS</i>	16.8%	13.9%	-1.6 (-6.7,3.5)	7.4%	9.2%	0.8 (-4.3,6.0)
<i>Baseline characteristics[±]:</i>						
<i>Disease duration, years (mean, SD)</i>	10.7 (10.7)	9.5 (10.1)	-1.0 (-2.7,0.7)	9.8 (12.5)	9.5 (10.1)	-0.2 (-3.1,2.6)
<i>HAQ, VAS scale (mean, SD)</i>	1.0 (0.6)	0.9 (0.6)	0.0 (-0.1,0.1)	0.9 (0.6)	0.9 (0.6)	-0.1 (-0.2,0.1)
<i>ESR,mm/h (mean, SD)</i>	22 (20)	23 (20)	0.4 (-2.4,3.1)	19 (19)	20 (18)	-0.3 (-3.7,3.1)

<i>CRP,mg/dl (mean, SD)</i>	18 (28)	15 (26)	-0.7 (-5.5,4.1)	11 (14)	12 (18)	1.3 (-2.1,4.6)
<i>Pain§,VAS scale (mean, SD)</i>	55 (26)	55 (24)	-1.2 (-5.5,3.0)	56 (22)	55 (24)	-0.8 (-6.0,4.5)
<i>Concomitant use of (%):</i>						
<i>MTX</i>	204 (68.7)	246 (56.9)	-0.1 (-6.3,6.0)	42 (57.5)	409 (51.9)	-1.2 (-12.1,9.7)
<i>Non-MTX csDMARDs</i>	40 (13.5)	68 (15.7)	4.4 (-1.4,10.1)	7 (9.6)	142 (18.0)	7.3 (-1.0,15.5)
<i>Oral corticosteroids (%)</i>	90 (30.3)	136 (31.5)	0.2 (-7.1,7.4)	20 (27.4)	245 (31.1)	2.5 (-6.9,11.8)
<i>NSAIDs (%)</i>	78 (26.3)	126 (29.2)	5.5 (-2.9,13.9)	18 (24.7)	219 (27.8)	1.2 (-10.6,12.9)

Abbreviations: HAQ = Health Assessment Questionnaire Disability Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; MTX = methotrexate, DMARDs = disease-modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drug.

§ Pain was measured on the Visual analogue scale (VAS)

± Information on baseline characteristics is collected from the visit closest to the date of start of treatment, among all the visits that occurred between 90 days prior and 30 days after the prescription. Visits in this range that occurred after any stop of the treatment under study were excluded.

*Mean differences are mutually adjusted, and additionally adjusted for region.

Table A2: Disease characteristics of patients switching from a non-originator bDMARD starting infliximab between March 1st 2015 and December 31th 2016, or etanercept between 1 April 2016 and December 31th 2016 in Sweden. Mean differences of biosimilar vs. originator were estimated using multivariable linear regression models, adjusted for all other variables and region.

	<i>Infliximab</i>			<i>Etanercept</i>		
	Originator	Biosimilar	Mean difference*	Originator	Biosimilar	Mean difference*
<i>N</i>	140	198		121	362	
<i>Age, year (mean, SD)</i>	54 (15)	50 (15)	-3.21 [-7.29,0.88]	54 (16)	54 (14)	2.77 [-0.74,6.29]
<i>Gender (%)</i>	89 (63.57)	147 (74.24)	2.64 [-11.41,16.69]	94 (77.69)	231 (63.81)	-1.41 [-12.95,10.13]
<i>Indication (%):</i>						
<i>RA</i>	41.43%	44.44%	1.07 [-10.09,12.22]	63.64%	54.42%	-13.82 [-26.85,-0.79]
<i>PsA</i>	22.14%	23.74%	-2.86 [-15.61,9.89]	18.18%	20.44%	2.60 [-4.77,9.96]
<i>SpA</i>	20.00%	22.22%	-2.46 [-12.64,7.72]	10.74%	14.92%	7.45 [-0.10,15.00]
<i>AS</i>	16.43%	9.60%	4.25 [-2.94,11.45]	7.44%	10.22%	3.77 [-1.14,8.69]
<i>Disease duration, year (mean, SD)</i>	15.67 (10.70)	12.27 (10.94)	-3.32 [-6.48,-0.16]	14.20 (9.83)	14.01 (11.92)	-1.88 [-4.34,0.58]
<i>HAQ, VAS scale (mean, SD)</i>	1.04 (0.65)	1.17 (0.56)	0.15 [-0.05,0.35]	0.93 (0.59)	1.02 (0.63)	-0.03 [-0.16,0.10]
<i>ESR,mm/h (mean, SD)</i>	22 (23)	20 (20)	1.23 [-5.57,8.03]	20 (18)	21 (20)	0.46 [-2.69,3.61]

CRP,mg/dl (mean, SD)	13 (20)	10 (18)	-1.44 [-7.78,4.89]	11 (20)	13 (20)	-0.98 [-5.18,3.23]
Pain§,VAS scale (mean, SD)	60 (25)	58 (23)	-5.96 [-11.54,-0.39]	50 (27)	58 (26)	6.98 [0.75,13.20]
Concomitant use of (%):						
MTX	41 (44.09)	76 (45.24)	-1.15 [-12.79,10.49]	35 (39.33)	146 (48.67)	14.26 [1.17,27.36]
Non-MTX csDMARDs	9 (9.68)	17 (10.12)	0.20 [-9.20,9.61]	9 (10.11)	32 (10.67)	1.49 [-6.60,9.58]
Oral corticosteroids (%)	21 (22.58)	62 (36.90)	15.69 [3.80,27.59]	25 (28.09)	99 (33.00)	0.58 [-10.98,12.14]
NSAIDs (%)	38 (40.86)	52 (30.95)	-7.47 [-23.57,8.63]	28 (31.46)	98 (32.67)	0.78 [-12.79,14.34]

Abbreviations: HAQ = Health Assessment Questionnaire Disability Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; MTX = methotrexate, DMARDs = disease-modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drug.

§ Pain was measured on the Visual analogue scale (VAS)

± Information on baseline characteristics is collected from the visit closest to the date of start of treatment, among all the visits that occurred between 90 days prior and 30 days after the prescription. Visits in this range that occurred after any stop of the treatment under study were excluded.

*Mean differences are mutually adjusted, and additionally adjusted for region.

Table A3: Regional differences between patients starting a biosimilar or the originator of infliximab between 1 March 2015 and 31 December 2016, or etanercept between 1 April 2016 and 31 December 2016. All regions except the south region in Sweden had agreements prioritizing use and better prize for Remicade when the infliximab biosimilars were introduced.

	Infliximab			Etanercept		
	Originator	Biosimilar	Mean difference*	Originator	Biosimilar	Mean difference *
Biological-naïve patients						
Norra	14 (4.1)	15 (2.9)	-1.69 [-4.40,1.03]	14 (14.7)	51 (5.5)	-3.56 (-10.17,3.05)
Stockholm	18 (5.3)	120 (22.8)	13.73 (8.90,18.56)	9 (9.5)	198 (21.2)	11.27 (4.32,18.21)
Sydöstra	74 (21.8)	55 (10.5)	-9.80 (-15.37,-4.24)	8 (8.4)	118 (12.6)	1.92 (-5.22,9.06)
Södra	14 (4.1)	135 (25.7)	20.29 (14.35,26.23)	13 (13.7)	219 (23.5)	5.83 (-4.26,15.91)
Uppsala-Örebro	63 (18.6)	84 (16.0)	-2.28 (-9.07,4.51)	31 (32.6)	257 (27.5)	-4.24 (-18.29,9.80)
Västsvenska	156 (46.0)	117 (22.2)	-20.25 (-27.27,-13.24)	20 (21.1)	90 (9.6)	-11.21 (-19.90,-2.53)
Patients switching from other molecules						
Norra	9 (6.43)	10 (5.05)	-4.18 [-10.62,2.27]	8 (6.61)	25 (6.91)	-0.48 [-6.46,5.49]
Stockholm	12 (8.57)	44 (22.22)	16.97 [5.40,28.54]	24 (19.83)	71 (19.61)	-6.32 [-16.75,4.11]
Sydöstra	22 (15.71)	9 (4.55)	-7.62 [-16.87,1.62]	11 (9.09)	65 (17.96)	10.52 [1.19,19.84]
Södra	34 (24.29)	76 (38.38)	6.41 [-6.91,19.73]	25 (20.66)	62 (17.13)	-1.03 [-12.40,10.35]
Uppsala-Örebro	43 (30.71)	46 (23.23)	-7.32 [-21.02,6.37]	37 (30.58)	73 (20.17)	-8.96 [-19.59,1.68]
Västsvenska	20 (14.29)	13 (6.57)	-4.26 [-13.37,4.85]	16 (13.22)	66 (18.23)	6.27 [-3.78,16.32]
Non-medical switchers						

Norra	165 (6.24)	63 (11.91)	5.38 [1.69,9.07]	557 (9.53)	121 (10.35)	1.73 [0.18,3.28]
Stockholm	237 (8.96)	41 (7.75)	-1.88 [-4.82,1.06]	1389 (23.76)	283 (24.21)	1.98 [-0.91,4.87]
Sydöstra	426 (16.11)	1 (0.19)	-14.63 [-16.49,- 12.76]	394 (6.74)	171 (14.63)	7.42 [5.19,9.65]
Södra	271 (10.25)	281 (53.12)	39.35 [36.09,42.61]	1329 (22.74)	129 (11.04)	-11.24 [-13.41,-9.06]
Uppsala- Örebro	515 (19.47)	138 (26.09)	6.82 [2.69,10.96]	1520 (26.01)	457 (39.09)	10.83 [7.95,13.71]
Västsvenska	1031 (38.98)	5 (0.95)	-35.04 [-37.47,- 32.61]	656 (11.22)	8 (0.68)	-10.73 [-11.83,-9.63]

*Adjusted for age, gender, indication, and baseline disease characteristics such as disease duration, time on originator (only within strata (ii)), HAQ (Health Assessment Questionnaire disability index), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein level), pain and concomitant use of metrothexate (MTX), non-MTX csDMARDs, oral corticosteroids and NSAIDs (non-steroidal anti-inflammatory drugs)