Utilisation patterns and clinical impact of the introduction of infliximab-biosimilar in Tuscany, Italy: real world evidence following the recommendation of switching for non-medical reasons

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Abstract

Objective

This study was aimed at assessing the impact of a non-medical recommendation on drug-utilisation patterns and clinical outcomes in a central Region of Italy (Tuscany).

Methods

We performed a pre-post study on data collected in Tuscan healthcare administrative databases. We included patients with diagnosis of rheumatoid arthritis, or psoriatic arthritis, or ankylosing spondylitis, or ulcerative colitis, or Crohn's disease, or psoriasis. The first analysis compared patients treated with infliximab on January 1st, 2013 (originator only available) to those on January 1st, 2016 (both originator and biosimilar available). The second analysis compared infliximab-originator users with infliximab-biosimilar ones. Adjusted odds ratios (OR) of persistence on treatment, Emergency Department (ED) admissions, hospitalisations and specialist visits were calculated.

Results

The first analysis included 606 patients and the second 434. In both analyses, we did not observe any significant difference in persistence. In the first analysis, the 2016 infliximab-originator cohort showed a significant association with the risk of having at least one ED admission (OR 1.54, 95% CI 1.02 to 2.31). A significant difference of accessing a specialist visit (more frequently rheumatologic) was observed in the 2016 cohort (OR 1.52, 95% CI 1.05 to 2.20). In the second analysis, the risk of having at least one hospitalisation decreased significantly in switchers to infliximab-biosimilar (OR 0.49, 95% CI 0.26 to 0.96).

Conclusion

Our study showed no relevant changes in the clinical outcomes following the introduction of infliximab-biosimilar. The few observed differences observed can be explained mainly by a selective switching to infliximab-biosimilar in patients with lower burden of disease.

Key words

biosimilar pharmaceuticals, disease-modifying anti-rheumatic drugs, drug utilisation, evidence-based medicine, rheumatoid arthritis

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Introduction

Immune-mediated inflammatory diseases (IMIDs) are a cluster of disabling disorders featuring inflammatory conditions, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, ulcerative colitis (UC), and Crohn's disease (CD) (1). Biological disease-modifying antirheumatic drugs (DMARDs) play a pivotal role in the management of IMIDs, controlling tissue inflammatory damage and disease progression (2, 3). However, these medications are characterised by high costs, possibly leading to patient access restriction to treatments.

Over the last years, the introduction of biosimilar drugs into clinical practice has represented a cost saving chance for Healthcare systems (4). This economic benefit originates from a simplification of the marketing authorisation process, as compared with originators (5). However, prescribers and healthcare professionals may perceive this shortening of the development process as a quality issue, with consequent uncertainties surrounding the effectiveness and safety of the biosimilar products (6-9). In this scenario, real world data could represent an important tool for healthcare professionals to improve their awareness towards biosimilars and to develop a more confident prescription of these drugs (10).

National and local Healthcare Authorities have implemented incentive policies to promote biosimilar prescription (11). In 2010, the Tuscan Regional Healthcare Authority recommended clinicians to prescribe medicinal products subjected to regional purchase contracts (12). In 2015, this recommendation touched infliximab-biosimilar, the first biosimilar available among anti-tumour necrosis factor (TNF) DMARDs, favoring its prescription to naïve patients and the switching for non-medical reasons in those under infliximab-originator treatment. In the present study, we have assessed the impact of this recommendation on drug-utilisation patterns and clinical outcomes.

Methods

Data source

We used data recorded in the Tuscan administrative healthcare database. This includes data from January 2004 and encompasses the several databases collecting administrative information from routine healthcare services: drug dispensing, specialist visits, hospitalisations, and access to the Emergency Department (ED). Dispensing of infliximab was retrieved from the drug-dispensing database and identified by the Anatomical Therapeutic Chemical code and the marketing authorisation codes. Infliximab therapeutic indications were retrieved from the hospital discharge records and ED admission database, and selected by the International Classification of Diseases, ninth edition. From the database of specialist encounters, rheumatologic, gastroenterological and dermatological visits were retrieved from the database of specialist encounters, using the local specialty codes.

Study design and study cohort

We applied a pre-post design to study the impact of the recommendation. We performed two distinct analyses (Fig. 1). In the first analysis, we focused on both infliximab-originator and infliximab-biosimilar, and we selected Tuscan patients treated with infliximab on January 1st, 2013 (2013 cohort), when only infliximab-originator was available, and January 1st, 2016 (2016 cohort), when infliximab-biosimilar had been already introduced into therapy, with at least one year of records in the databases prior to cohort entry (look-back period). We included adult patients having at least one record of infliximab dispensing and one disease among RA, AS, PsA, CD, UC and psoriasis in the look-back period. In the second analysis, we investigated patients on the basis of their treatment (*i.e.* infliximab-originator or infliximab-biosimilar), and we included adult Tuscan patients treated with infliximab-originator on January 1st, 2013 and with infliximab-biosimilar on January 1st, 2016. In the look-back period, at least a diagnosis of RA, AS, PsA, CD, UC or psoriasis and one dispensing of infliximab had been retrieved. Based on these criteria, the same patient could have been included in both the 2013 and 2016 cohort (first analysis) as well as in both the origina-

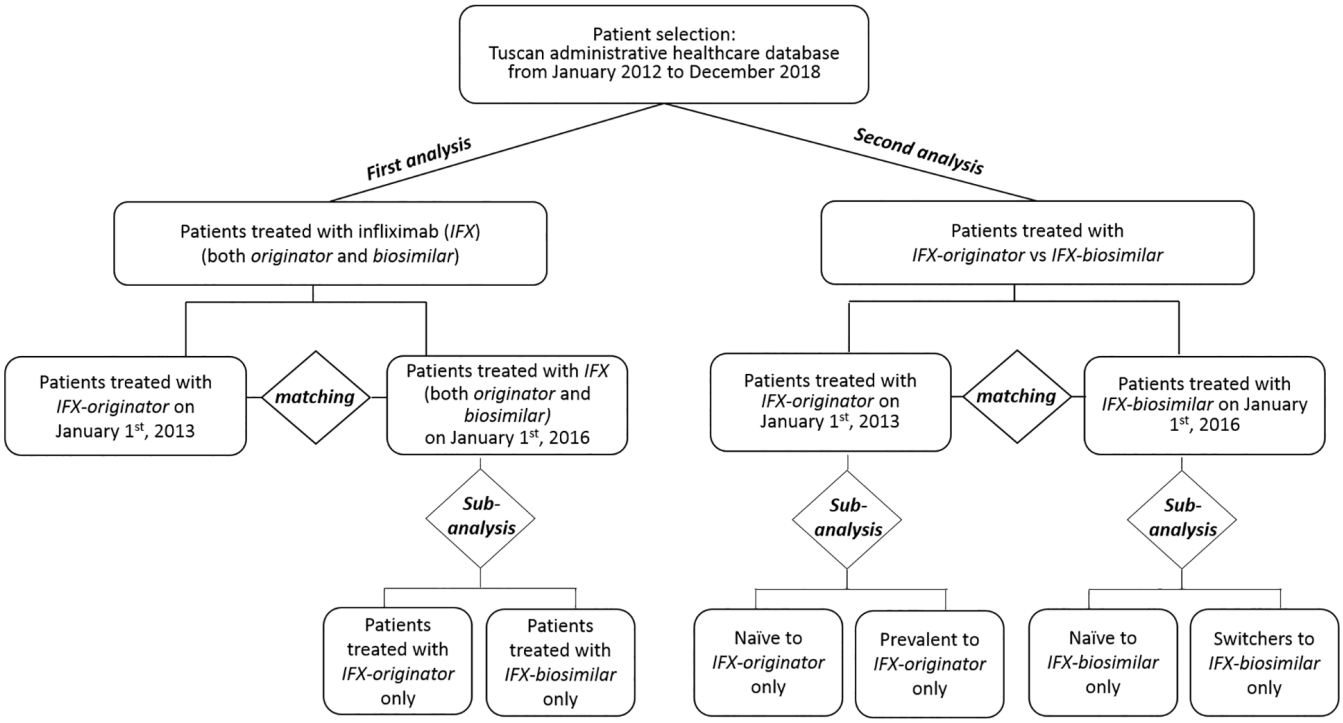

Fig. 1. Study flow chart: selection of patients included in the two analyses.

tor and the biosimilar cohort (second analysis). In the two analyses, the patients were observed for 2 years.

Outcomes

The primary outcomes of this study were: persistence, admission to the ED or hospitalisation, access to the ED, hospitalisation, and specialist visits (overall and stratified by both therapeutic area and clinical indications of infliximab). A patient was defined persistent to infliximab in the period covered from the first prescription at the cohort entry to the last one recorded, with a gap period ≤3 months (13). Discontinuation was defined as the lack of infliximab prescription in a period >3 months. Switching and swapping were defined by the prescription of another anti-TNF DMARD or a non-anti-TNF biologic DMARD, respectively.

Statistical analysis

- First analysis

We performed a propensity score (PS) matching to balance the "2013 cohort" and the "2016 cohort" according to the subject baseline characteristics, including gender, age, disease, and duration of treatment. The variable "disease" patients were classified in twelve different categories: patients with only one disease (RA, AS, PsA, CD, UC and psoriasis), combinations of two diseases (two rheumatologic, two gastroenterological, rheumatologic and gastroenterological, rheumatologic and dermatological, gastroenterological and dermatological), and multiple diseases. We estimated the association between the occurrence of the outcomes of interest and the belonging to the "2016 cohort" using the "2013 cohort" as reference.

In a sub-analysis, we classified the patients of the 2016 cohort into two mutually exclusive groups based on their treatment with infliximab-originator or infliximab-biosimilar at cohort entry. We estimated the association between the occurrence of the outcomes of interest and the belonging to the "2016 infliximab-originator cohort" or the "2016 infliximab-biosimilar cohort" using the "2013 cohort" as reference.

- Second analysis

We performed a PS matching to balance the "Originator cohort" and the "Biosimilar cohort" according to gender, age, infliximab indications, and treatment duration. We estimated the association between the occurrence of the outcomes of interest and the belonging to the "Biosimilar cohort" using the "Originator cohort" as reference.

In a sub-analysis, patients of the two cohorts were categorised according to infliximab treatment. Patients were classified as naïve if they had their first ever record of infliximab use in the year before the cohort entry. Patients in the infliximab-originator and infliximab-biosimilar group were defined as prevalent and switchers, respectively, when they had more than one year of history use of infliximab. We estimated the association between the occurrence of the outcomes of interest and the belonging to the "biosimilar switcher cohort" using the "originator prevalent cohort" as reference, and the belonging to the "biosimilar naïve cohort" using the "originator naïve cohort" as reference.

- First and second analyses

We reported the results as mean and standard deviation for continuous variables and compared the means using the t-test; and as absolute number and percentage for categorical variables and compared the distributions using the chi-square test. A p-value <0.05 was considered statistically significant.

We matched the cohorts using the method of nearest neighbour match-

Table I. Characteristics of the included patients after Propensity Score matching; the first analysis.

	2013 cohort ¶, §	2016 cohort ¶					
		Overall §	*p*-value #,1	Infliximab-originator	*p*-value #,2	Infliximab-biosimilar	*p*-value #,3
Patients, n	303	303		169		134	
Male, n (%)	178 (58.7)	162 (53.5)	0.220	91 (53.8)	0.350	71 (53.0)	0.390
Age, mean (SD)	38.9 (17.6)	39.7 (18.3)	0.606	42.6 (18.5)	0.031	35.9 (17.6)	0.102
Duration of treatment in years, mean (SD)	2.1 (2.2)	2.4 (2.4)	0.131	3.0 (2.3)	<0.001	1.7 (2.5)	0.093
Disease, n (%)			0.956		0.129		0.739
Only one disease							
Rheumatoid arthritis	35 (11.6)	42 (13.9)		28 (16.6)		14 (10.4)	
Psoriatic arthritis	21 (6.9)	26 (8.6)		18 (10.7)		8 (6.0)	
Ankylosing spondylitis	43 (14.2)	45 (14.9)		35 (20.7)		10 (7.5)	
Ulcerative colitis	41 (13.5)	32 (10.6)		13 (7.7)		19 (14.2)	
Crohn's disease	35 (11.6)	34 (11.2)		15 (8.9)		19 (14.2)	
Psoriasis	10 (3.3)	11 (3.6)		5 (3.0)		6 (4.5)	
Two diseases							
Two gastroenterological	31 (10.2)	37 (12.2)		18 (10.7)		19 (14.2)	
Two rheumatologic	20 (6.6)	16 (5.3)		7 (4.1)		9 (6.7)	
Gastroenterological and dermatological	3 (1.0)	2 (0.7)		0 (0.0)		2 (1.5)	
Rheumatologic and dermatological	23 (7.6)	21 (6.9)		7 (4.1)		14 (10.4)	
Rheumatologic and gastroenterological	19 (6.3)	37 (12.2)		8 (4.7)		6 (4.5)	
Multiple diseases							
Three or more	22 (7.3)	23 (7.6)		15 (8.9)		8 (6.0)	

¶The 2013 cohort and 2016 cohort included patients treated with infliximab on January 1st, 2013 and January 1st, 2016, respectively.
§Patients were matched for gender, age, disease, and duration of infliximab treatment in years.
#*p*-values were estimated by t-test and chi-squared test for comparing means and proportions, respectively; [1]comparison between the 2013 cohort and the 2016 cohort; [2]comparison between the 2013 cohort and the 2016 infliximab-originator cohort; [3]comparison between the 2013 cohort and the 2016 infliximab-biosimilar cohort. n: number; SD: standard deviation.

Table II. Patterns of infliximab treatment, distribution and odds ratio of persistence; the first analysis.

	2013 cohort ¶,§[2]	016 cohort¶					
	n (%)	Overall §,°,a n (%)	OR #,1 (95% CI)	Infliximab - originator °,b n (%)	OR #,2 (95% CI)	Infliximab-biosimilar °,c n (%)	OR #,3 (95% CI)
All patients	303	303		169		134	
Persistent patients	157 (51.8)	148 (48.8)	0.84 (0.60 to 1.18)	89 (52.7)	0.89 (0.59 to 1.34)	59 (44.0)	0.82 (0.52 to 1.27)
Discontinuing patients	87 (28.7)	90 (29.7)		46 (27.2)		44 (32.8)	
Patients restarting infliximab[c]	15 (5.0)	16 (5.3)		11 (6.5)		5 (3.7)	
Patients switching to another anti-TNF	42 (13.9)	41 (13.5)		18 (10.7)		23 (17.2)	
Patients swapping to a non-anti-TNF biologic DMARD	2 (0.7)	8 (2.6)		5 (3.0)		3 (2.2)	

¶The 2013 cohort and 2016 cohort included patients treated with infliximab on January 1st, 2013 and January 1st, 2016, respectively.
§Patients were matched for gender, age, disease, and duration of infliximab treatment in years.
°*p*-value estimated by t-test and chi-squared test used for comparing means and proportions, respectively; [a]comparison between the overall 2016 cohort and the 2013 cohort; [b]comparison between the 2016 infliximab-originator cohort and the 2013 cohort (infliximab-originator only); [c]comparison between the 2016 infliximab-biosimilar cohort and the 2013 cohort.
#OR were calculated by logistic regression models and adjusted for gender, age, disease, and duration of treatment in years; [1] OR for the 2016 cohort compared with the 2013 cohort; [2]OR for the 2016 infliximab-originator cohort compared with the 2013 cohort (infliximab-originator only); [3]OR for the 2016 infliximab-biosimilar cohort compared with the 2013 cohort.
[c]After ≥3 months of infliximab discontinuation.
CI: confidence interval; DMARD: disease-modifying anti-rheumatic drug; n: number; OR: odds ratio; TNF: tumour necrosis factor.

ing with a caliper width equal to 0.2. We estimated the associations by calculating the odds ratio (OR) and 95% Confidence Interval (CI) using logistic regression models adjusted for the PS matching variables. An OR was considered statistically significant if the corresponding CI did not include the unit. All statistical analyses were performed using RStudio v. 1.1.463.

Results

First analysis

We included overall 888 patients (Supplementary File, Fig. S1); 454 patients were in the 2013 cohort and 434 in the 2016 cohort. The distribution of baseline characteristics of the two cohorts before matching is summarised in Supplementary Table S1.

After matching, 303 patients remained in each group (Table I). Patients receiving infliximab-originator in the 2016 cohort were 169 (55.8%). In the 2016

infliximab-biosimilar cohort, gastrointestinal indications were the most frequently recorded, while in the 2016 infliximab-originator cohort the most frequently reported indications were the rheumatologic ones.

Persistence

We did not observe any significant difference in persistence between the cohorts, as well as in the distribution of discontinuation, infliximab restarting, switching to another anti-TNF and swapping to a non-anti-TNF biologic DMARD (Table II). These results were similar in the infliximab-originator and infliximab-biosimilar 2016 cohorts. The distribution of persistent patients according to diseases is reported in Supplementary Table S2.

Emergency Department admissions and hospitalisations

No significant difference was observed between the cohorts with regard for the ED admissions and/or hospitalisation (Table III). The 2016 infliximab-originator cohort showed a significant association with ED admission as compared with the 2013 cohort (OR 1.54, 95% CI 1.02 to 2.31). The most reported causes of ED admissions and hospitalisations are shown in Supplementary Table S3.

Specialist visits

As compared with the 2013 cohort, a significant association between specialist visits and the 2016 cohort was observed (OR 1.83, 95% CI 1.25 to 2.68, Table III). In particular, a direct association was found for rheumatologic visits (OR 1.52, 95% CI 1.05 to 2.20) even including patients with only rheumatologic indications (OR 1.73, 95% CI 1.13 to 2.66). The results were con-

Table III. Distribution and odds ratio of the overall accesses, Emergency Department admissions, hospitalisations and specialist visits; the first analysis.

	2013 cohort ¶,§	2016 cohort ¶					
	n (%)	Overall § n (%)	OR #,1 (95% CI)	Infliximab-originator n (%)	OR #,2 (95% CI)	Infliximab-biosimilar n (%)	OR #,3 (95% CI)
All patients	303	303		169		134	
Patients with at least one ED admission or hospitalisation	171 (56.4)	176 (58.1)	1.10 (0.79 to 1.54)	100 (59.2)	1.25 (0.83 to 1.88)	76 (56.7)	0.94 (0.61 to 1.44)
Patients with at least one ED admission	117 (38.6)	135 (44.6)	1.31 (0.94 to 1.82)	78 (46.2)	1.54 (1.02 to 2.31)	57 (42.5)	1.13 (0.74 to 1.73)
Patients with at least one hospitalisation	111 (36.6)	115 (38.0)	1.08 (0.76 to 1.52)	64 (37.9)	1.10 (0.72 to 1.68)	51 (38.1)	0.93 (0.59 to 1.47)
Patients with at least one specialist visit	210 (69.3)	242 (79.9)	1.83 (1.25 to 2.68)	137 (81.1)	2.07 (1.28 to 3.35)	105 (78.4)	1.54 (0.94 to 2.53)
Patients with at least one rheumatologic visit	111 (36.6)	139 (45.9)	1.52 (1.05 to 2.20)	96 (56.8)	2.06 (1.32 to 3.21)	43 (32.1)	0.96 (0.59 to 1.58)
Patients with psoriatic arthritis/rheumatoid arthritis/ankylosing spondylitis	93 (51.1)	122 (65.2)	1.73 (1.13 to 2.66)	86 (72.9)	2.37 (1.41 to 3.09)	36 (52.2)	1.06 (0.59 to 1.90)
Patients with other therapeutic indications	18 (14.9)	17 (14.7)	1.00 (0.47 to 2.11)	10 (19.6)	1.40 (0.56 to 3.49)	7 (10.8)	0.73 (0.27 to 1.94)
Patients with at least one gastroenterological visit	89 (29.4)	93 (30.7)	1.39 (0.88 to 2.20)	38 (22.5)	1.05 (0.60 to 1.82)	55 (41.0)	1.e
Patients with Crohn's disease/ulcerative colitis	81 (59.1)	84 (63.6)	1.72 (0.80 to 3.69)	34 (54.0)	1.33 (0.53 to 3.36)	50 (72.5)	2.82 (1.08 to 7.34)
Patients with other therapeutic indications	8 (4.8)	9 (5.3)	1.25 (0.69 to 2.26)	4 (3.8)	1.22 (0.56 to 2.68)	5 (7.7)	1.33 (0.64 to 2.79)
Patients with at least one dermatological visit	72 (23.8)	92 (30.4)	1.41 (0.96 to 2.06)	46 (27.2)	1.19 (0.75 to 1.89)	56 (34.3)	1.73 (1.06 to 2.82)
Patients with psoriasis	21 (42.0)	22 (52.4)	1.47 (0.91 to 2.37)	4 (23.5)	1.18 (0.67 to 2.08)	18 (72.0)	2.00 (1.05 to 3.80)
Patients with other therapeutic indications	51 (20.2)	70 (26.8)	1.36 (0.73 to 2.57)	42 (27.6)	1.28 (0.57 to 2.86)	28 (25.7)	1.45 (0.68 to 3.10)

¶The 2013 cohort and 2016 cohort included patients treated with infliximab on January 1st, 2013 and January 1st, 2016, respectively.

§Patients were matched for gender, age, disease, and duration of infliximab treatment in years.

#OR were calculated by logistic regression models and adjusted for gender, age, disease, and duration of treatment in years; [1] OR for the 2016 cohort compared with the 2013 cohort; [2]OR for the 2016 infliximab-originator cohort compared with the 2013 cohort (infliximab-originator only); [3]OR for the 2016 infliximab-biosimilar cohort compared with the 2013 cohort.

CI: confidence interval; DMARD: disease-modifying anti-rheumatic drug; ED: Emergency Department; n: number; OR: odds ratio; TNF: tumour necrosis factor.

Table IV. Characteristics of the included patients after Propensity Score matching; the second analysis.

	Originator[¶]			Biosimilar[¶]					
	Overall [§]	Naïve	Prevalent	Overall [§]	*p*-value [#,1]	Naïve	*p*-value [#,2]	Switchers	*p*-value [#,3]
Patients, n	265	85	180	169		78		91	
Male, n (%)	159 (60.0)	56 (65.9)	103 (57.2)	94 (55.6)	0.422	33 (42.3)	0.004	61 (77.0)	0.153
Age, mean (SD)	37.5 (17.6)	34.11 (18.54)	39.14 (16.95)	36.4 (17.2)	0.495	35.0 (19.0)	0.752	37.48 (15.56)	0.434
Duration of treatment in years, mean (SD)	1.8 (2.0)	0	2.62 (1.96)	2.1 (2.9)	0.141	0	-	3.95 (2.84)	<0.001
Disease, n (%)					0.988		0.026		0.225
Only one disease									
Rheumatoid arthritis	26 (9.8)	1 (1.2)	25 (13.9)	15 (8.9)		7 (9.0)		8 (8.8)	
Psoriatic arthritis	16 (6.0)	4 (4.7)	12 (6.7)	10 (5.9)		4 (5.1)		6 (6.6)	
Ankylosing spondylitis	32 (12.1)	3 (3.5)	29 (16.1)	14 (8.3)		6 (7.7)		8 (8.8)	
Ulcerative colitis	41 (15.5)	30 (35.5)	11 (6.1)	29 (17.2)		19 (24.4)		10 (11.0)	
Crohn's disease	34 (12.8)	23 (27.1)	11 (6.1)	27 (16.0)		14 (17.9)		13 (14.3)	
Psoriasis	14 (5.3)	0 (0.0)	14 (7.8)	7 (4.1)		0 (0.0)		7 (7.7)	
Two diseases									
Two gastroenterological	31 (11.7)	14 (16.5)	17 (9.4)	21 (12.4)		16 (20.5)		5 (5.5)	
Two rheumatologic	15 (5.7)	0 (0.0)	15 (8.3)	10 (5.9)		5 (6.4)		5 (5.5)	
Gastroenterological and dermatological	4 (1.5)	3 (3.5)	1 (0.6)	2 (1.2)		0		2 (2.2)	
Rheumatologic and dermatological	21 (7.9)	0 (0.0)	21 (11.7)	15 (8.9)		2 (2.6)		13 (14.3)	
Rheumatologic and gastroenterological	17 (6.4)	3 (3.5)	14 (7.8)	9 (5.3)		2 (2.6)		7 (7.7)	
Multiple diseases									
Three or more	14 (5.3)	4 (4.7)	10 (5.6)	10 (5.9)		3 (3.8)		7 (7.7)	

[¶]The originator cohort included patients treated with infliximab-originator on January 1st, 2013 and the biosimilar cohort included those treated with infliximab-biosimilar on January 1st, 2016

[§]Patients were matched for gender, age, disease, and duration of infliximab treatment in years

[#]*p*-values were estimated by t-test and chi-squared test for comparing means and proportions, respectively; [1]comparison between the overall biosimilar cohort and the overall originator cohort; [2]comparison between the naïve biosimilar cohort and the naïve originator cohort; [3]comparison between the switcher biosimilar cohort and the prevalent originator cohort.

n: number; SD: standard deviation

Table V. Patterns of infliximab treatment, distributions and odds ratio of persistence; the second analysis.

	Originator[¶]				Biosimilar[¶]				
	Overall [§] n (%)	Naïve n (%)	Prevalent n (%)	Overall [§,°,a] n (%)	OR [#,1] (95% CI)	Naïve [°,b] n (%)	OR [#,2] (95% CI)	Switchers [°,c] n (%)	OR [#,3] (95% CI)
All patients	265	85	180	169		78		91	
Persistent patients	145 (54.7)	27 (31.8)	118 (65.6)	78 (46.2)	0.70 (0.46 to 1.06)	26 (33.2)	1.26 (0.59 to 2.67)	52 (57.1)	0.68 (0.37 to 1.23)
Discontinuing patients	69 (26.0)	38 (44.7)	31 (17.2)	54 (32.0)		31 (39.7)		23 (25.3)	
Patients restarting infliximab[c]	17 (6.4)	6 (7.1)	11 (6.1)	6 (3.6)		6 (7.7)		0[**]	
Patients switching to another anti-TNF	33 (12.5)	14 (16.5)	19 (10.6)	28 (16.6)		13 (16.7)		15 (16.5)	
Patients swapping to a non-anti-TNF biologic DMARD	1 (0.4)	0 (0.0)	1 (0.6)	3 (1.8)		2 (2.6)		1 (1.1)	

[¶]The originator cohort included patients treated with infliximab-originator on January 1st, 2013 and the biosimilar cohort included those treated with infliximab-biosimilar on January 1st, 2016.

[§]Patients were matched for gender, age, disease, and duration of infliximab treatment in years.

[°]*p*-values were estimated by t-test and chi-squared test for comparing means and proportions, respectively; [a]comparison between the overall biosimilar cohort and the overall originator cohort; [b]comparison between the naïve biosimilar cohort and the naïve originator cohort; [c]comparison between the switcher biosimilar cohort and the prevalent originator cohort.

[**]*p*-value <0.05.

[#]ORs were calculated by logistic regression models and adjusted for gender, age, disease, and duration of treatment in years; [1]OR for the overall biosimilar cohort compared with the originator cohort; [2]OR for the naïve biosimilar cohort compared with the originator cohort; [3]OR for the switchers biosimilar cohort compared with the originator cohort.

[c]After ≥3 months of infliximab discontinuation.

CI: confidence interval; DMARD: disease-modifying anti-rheumatic drug; n: number; OR: odds ratio; TNF: tumour necrosis factor.

firmed for infliximab-originator users (OR of specialist visits was 2.07, 95% CI 1.28 to 3.35; OR of rheumatologic visits was 2.06, 95% CI 1.32 to 3.21). By contrast, for the 2016 infliximab-biosimilar cohort, a significant association was found for gastroenterological and dermatological visits in the respective therapeutic indications belonging to these therapeutic area (OR 2.82, 95% CI 1.08 to 7.34; and OR 2.00, 95% CI 1.05 to 3.80, respectively). The minimum detectable OR values for the investigated outcomes have been displayed in Supplementary Table S4.

Second analysis

We included 625 patients overall (Suppl. Fig. S2), 454 patients treated with infliximab-originator and 171 patients treated with infliximab-biosimilar (Suppl. Table S5). In particular, 124 and 99 patients were naïve to infliximab treatment, respectively (p=0.556). After matching, 265 patients were included in the infliximab-originator cohort and 169 in the infliximab-biosimilar one (Table IV). Out of these, 78 patients were naïve to infliximab-biosimilar and 91 could be classified as switchers.

Persistence

No significant difference was observed in the persistence among infliximab-biosimilar users as compared with patients treated with infliximab-originator (Table V). These results were similar for naïve and switchers, with the exception of the distribution of patients restarting infliximab after a discontinuation period greater than 3 months (switchers n=0 *vs.* prevalent n=11). The distribution of persistent patients subdivided by categories of disease is reported in Supplementary Table S6.

Emergency Department admissions and hospitalisations

No association was observed between ED admissions and/or hospitalisations and infliximab-biosimilar users as compared with the infliximab-originator ones (Table VI). Of note, the association with hospitalisations was significant for switchers of the infliximab-biosimilar cohort (OR 0.49, 95% CI 0.26 to 0.96). The ED admission and hospitalisation causes are described in Supplementary Table S3.

Specialist visits

Patients treated with infliximab-biosimilar displayed a significant association with gastroenterological visits as compared with those treated with infliximab-originator, as well as restricting to Crohn's disease and ulcerative colitis indications (Table VI). We found a significant association with specialist visits for patients switching to infliximab-biosimilar, and we confirmed the findings related to the gastroenterological area.

The minimum detectable OR values for the investigated outcomes have been displayed in Supplementary Table S7.

Discussion

This study, performed by analysis of real world data, provides for the first time a complete picture of the impact of the recommendation to use infliximab-biosimilar for any indication, including information about the adherence of prescribers to such recommendation and the consequent clinical impact of infliximab use. Our results suggest that such recommendation did not affect significantly the investigated outcomes. These findings are in line with previous observational studies performed in the specific medical disciplines, displaying no significant differences in persistence (14-16), hospitalisations for any cause (17, 18) and specialist visits19 in patients exposed to infliximab-biosimilar, as compared with those treated with infliximab-originator. Indeed, current evidence about switching to infliximab-biosimilar, regardless of the medicinal product, suggests no effectiveness and safety issues in the investigated IMIDs (20, 21).

The recommendation issued by the Tuscan health authority resulted in a progressive increase in the prescription of infliximab-biosimilar, although a large proportion of patients remained under treatment with infliximab-originator. This observation leads to suppose that clinicians selected somehow the patients who were candidate to infliximab-biosimilar treatment. In particular, we hypothesise that physicians selected the patients with a potential high burden of disease to be maintained under treatment with the originator (*e.g.* older, p=0.031). Consistently with this view, the second analysis confirmed that patients switching to the biosimilar drug were potentially stable in disease, and indeed they were on treatment for a longer period than patients maintained to infliximab-originator, p<0.001. Notably, this attitude to channel patients with higher disease burden (and therefore potentially subjected to a higher frequency of adverse events) towards safer (or apparently safer) treatments has been already documented in the medical literature (channeling bias) (14, 22). In this scenario, we cannot exclude that the switching of the overall population, regardless of disease severity and/or co-morbidity, could have had a different impact on the study outcomes. Then, this medical approach, driven by clinical judgement, could have ensured no detectable changes in the routine clinical care. In our opinion, this could also explain on one hand the high proportion of specialist visits and ED admissions found in the first analysis among the 2016 infliximab-originator users, and on the other hand the protective effect of hospitalisations associated with switchers to infliximab-biosimilar observed in the second analysis.

Persistence on treatment resulted similar across groups and comparisons in the two analyses. In the matched cohorts, about the 50% of patients was persistent to infliximab over 2 years. This finding is in line with previous observational studies. One study, performed on rheumatoid arthritis patients followed up for 2 years, showed a proportion of persistent patients of about 40% (14) The other one found a range of persistent patients from 72% to 94% (15, 16, 23). However, these investigations were conducted on patients with specific indications of infliximab (*i.e.* rheumatologic (15, 23) or gastroenterological ([16] only) and had shorter follow-up periods. Only Yazici *et al.* (2018) (24) found a significant higher percentage of persistent patients in the group exposed to infliximab-originator than that observed in the group of switchers to infliximab-biosimilar

Table VI. Distribution and odds ratio of the overall accesses, Emergency Department admissions, hospitalisations and specialist visits; the second analysis.

	Originator[¶]			Biosimilar[¶]					
	Overall[§] n (%)	Naïve n (%)	Prevalent n (%)	Overall[§] n (%)	OR[#,1] (95% CI)	Naïve n (%)	OR[#,2] (95% CI)	Switchers n (%)	OR[#,3] (95% CI)
All patients	265	85	180	169		78		91	
Patients with at least one ED admission or hospitalisation	153 (57.7)	49 (57.6)	104 (57.8)	94 (55.6)	0.90 (0.60 to 1.35)	51 (65.4)	1.14 (0.55 to 2.37)	43 (47.3)	0.68 (0.39 to 1.20)
Patients with at least one hospitalisation	106 (40.0)	40 (47.1)	66 (37.6)	63 (37.3)	0.91 (0.60 to 1.39)	45 (57.7)	1.21 (0.60 to 2.45)	18 (19.8)	0.49 (0.26 to 0.96)
Patients with at least one ED admission	102 (38.5)	35 (41.2)	67 (37.2)	72 (42.6)	1.11 (0.74 to 1.66)	32 (41.0)	0.98 (0.48 to 1.98)	40 (44.0)	1.10 (0.61 to 1.98)
Patients with at least one specialist visit	191 (72.1)	75 (88.2)	116 (64.4)	134 (79.3)	1.52 (0.94 to 2.45)	63 (80.8)	0.50 (0.20 to 1.30)	71 (78.0)	1.97 (1.02 to 3.80)
Patients with at least one rheumatologic visit	92 (34.7)	20 (23.5)	72 (40.0)	56 (33.1)	1.02 (0.64 to 1.65)	29 (37.2)	1.06 0.43 to 2.61)	27 (29.7)	0.67 (0.34 to 1.31)
Patients with psoriatic arthritis or rheumatoid arthritis or ankylosing spondylitis	73 (54.2)	8 (9.41)	65 (36.1)	45 (52.1)	1.10 (0.61 to 1.99)	22 (75.9)	10.73 (1.14 to 101.02)	23 (42.6)	0.66 (0.30 to 1.43)
Patients with other therapeutic indications	19 (15.2)	12 (14.12)	7 (3.9)	11 (12.8)	0.85 (0.37 to 1.94)	7 (14.3)	0.84 (0.29 to 2.41)	4 (10.8)	0.63 (0.15 to 2.59)
Patients with at least one gastroenterological visit	85 (32.1)	61 (71.8)	24 (13.3)	77 (45.6)	2.33 (1.35 to 4.00)	37 (47.4)	0.46 (0.20 to 1.04)	40 (44.0)	11.81 (4.45 to 31.31)
Patients with Crohn's disease or ulcerative colitis	79 (59.4)	59 (69.41)	20 (11.1)	70 (75.3)	2.42 (1.30 to 4.53)	36 (69.2)	0.62 (0.27 to 1.45)	34 (82.9)	12.94 (3.81 to 43.94)
Patients with other therapeutic indications	6 (4.5)	2 (2.35)	4 (2.2)	7 (9.2)	2.26 (0.70 to 7.34)	1 (3.8)	NE	6 (12.0)	8.44 (1.48 to 48.16)
Patients with at least one dermatological visit	68 (25.7)	16 (18.8)	52 (28.9)	53 (31.4)	1.36 (0.84 to 2.18)	17 (21.8)	0.85 (0.35 to 2.02)	36 (39.6)	1.73 (0.88 to 3.41)
Patients with psoriasis	25 (53.2)	0	25 (13.9)	20 (71.4)	1.93 (0.60 to 6.24)	0 (0.0)	NE	20 (80.0)	5.14 (1.01 to 26.10)
Patients with other therapeutic indications	43 (19.7)	16 (18.82)	27 (15.0)	33 (23.4)	1.22 (0.72 to 2.07)	17 (22.7)	0.84 (0.35 to 2.02)	16 (24.2)	1.33 (0.60 to 2.98)

[¶]The originator cohort included patients treated with infliximab-originator on January 1st, 2013 and the biosimilar cohort included those treated with infliximab-biosimilar on January 1st, 2016.

[§]Patients were matched for gender, age, disease, and duration of infliximab treatment in years.

[#]OR were calculated by logistic regression models and adjusted for gender, age, disease, and duration of treatment in years; [1]OR for the overall biosimilar cohort compared with the overall originator cohort; [2]OR for the naïve biosimilar cohort compared with the naïve originator cohort; [3]OR for the switcher biosimilar cohort compared with the prevalent originator cohort.

CI: confidence interval; ED: Emergency Department; n: number; NE: not estimable; OR: odds ratio.

(66% *vs.* 13%, respectively; $p<0.001$). However, in that study, the calendar year of the cohort entry was not included among the matching variables, and this likely biased the results toward significance.

In the 2016 infliximab-biosimilar cohort, the percentage of patients swapping to a non-anti-TNF biologic DMARD, which could be considered as a proxy of occurrence of uncontrolled disease or safety issue, did not differ significantly (2.2%) from that of the 2016 infliximab-originator cohort (3.0%) and the 2013 cohort (0.7%). This was observed also in second analysis, where the trend of patients swapped to a non-anti-TNF biologic DMARD was consistent with that of the first analysis. Furthermore, the measure of restarting infliximab after a short interruption period could be a proxy of disease relapse, and in the first analysis, the percentage of these patients in the 2016 infliximab-biosimilar cohort was similar to that in the 2016 infliximab-originator cohort (6.5%) and the 2013 cohort (5.0%). By contrast, in the second analysis, no patients restarted infliximab-biosimilar among switchers. This could be interpreted as a different prescriptive behavior of physicians, preferring to switch (16.5%) or swap (1.1%) to other options when the disease relapsed in those patients already switched to the biosimilar drug.

In the first analysis, the 2016 infliximab cohort showed a significant increase in the overall specialist visits. This increase was apparently led by rheumatologic visits, particularly in patients with a rheumatologic disease. The subanalysis revealed that this observation involved mainly patients receiving the infliximab-originator, supporting our hypothesis that patients remaining under infliximab-originator treatment are likely those with a higher disease burden, as discussed above. By contrast, the 2016 infliximab-biosimilar cohort showed an increase in gastroenterological visits among patients with inflammatory bowel disease and of dermatological visits among both overall and

psoriatic patients. The second analysis showed that the increase in dermatologic and gastroenterological visits occurred mainly in patients who had been switched from the originator to biosimilar. In our opinion, the above findings could be explained by different undisclosed criteria of decision making by clinicians working in different therapeutic settings and with different patients. Glintborg *et al*. (2018) (19) showed no differences in the rate of specialist visits recorded in the Danish national clinical registry for patients with rheumatoid arthritis (DANBIO), after switching to infliximab-biosimilar from infliximab-originator in compliance with a national mandatory recommendation.

When the safety outcome was considered, we did not observe any substantial difference in the proportion of patients with at least one ED admission and/or hospitalisation for any cause. Only patients in the 2016 infliximab-originator cohort showed a significant association with ED admissions. We explain this result again with the possible selective maintenance of the originator in patients with high disease burden, as discussed above. The same explanation can be given also to account for the protective effect towards hospitalisations, as observed among switchers (likely with low disease burden) in the second analysis. To the best of our knowledge, only two retrospective cohort studies had evaluated previously the safety profile of infliximab-biosimilar *versus* infliximab-originator by assessing hospitalisations for any cause. In line with our results, these studies, performed on the French national healthcare administrative databases and focusing on gastroenterological diseases, did not show any significant difference in hospital admission among infliximab-naïve patients (17, 18).

The present study has several important point of strengths: first, when compared with available studies, it analysed a relatively large sample of infliximab users over a long follow-up period (2 years); second, it used data collected in the Tuscan administrative healthcare databases, and therefore the results provide real world evidence about the actual clinical use of infliximab-biosimilar. These population-based data sources are better representative of biosimilar utilisation patterns in the real world, and they are more suitable for evaluating accesses to healthcare services across all therapeutic areas than other data sources. Third, the prescription-level utilisation analysis of infliximab-biosimilar accounted in 2016, few months after its market entry, in comparison with a relatively historical cohort of infliximab-originator users referred to 2013, is a crucial strategy to detect differences in prescribing behaviour and related clinical outcomes. Fourth, since infliximab was the first biosimilar of its drug class, the experience highlighted by the present study could be helpful in future similar assessments focused on other biosimilar anti-TNF DMARDs that have been more recently introduced in the clinical use (etanercept and adalimumab).

Besides those classically related to observational studies, we must consider also other limitations. First, the data analysed in this study are possibly incomplete and uncertain, since they were recorded in administrative healthcare databases (25) which have been implemented mainly for reimbursement purposes. Therefore, misclassifications cannot be excluded. Second, the prescription level utilisation analysis does not allow to retrieve clinical information on patients' level (26), such as disease severity, that could be useful for a comprehensive interpretation of the results. Third, our findings apply to what has actually occurred in Tuscany, and thus these results cannot be generalised to other realities. Fourth, the elevated number of disease categories would have produced unreliable results not suitable for clinical use, thus the investigation of the impact of the recommendation upon stratification for each therapeutic indication was not performed. Fifth, the inclusion of multiple infliximab indications has introduced heterogeneity into the study population, and this could have also affected our findings as well. However, we tried to control all these limitations by PS matching and subsequent adjustments using relevant co-variates, such as the duration of infliximab treatment and infliximab indication. Through this, the assessment of the overall impact of the non-medical recommendation has been made possible.

In conclusion, our study describes carefully what occurred actually following the issue of recommendation for the use of infliximab-biosimilar for any indication, and suggests no relevant changes in persistence, ED admissions, and hospitalisations. In our opinion, these results reflect a selective approach of clinicians in prescribing infliximab-biosimilar according to their clinical judgment, based on disease burden in individual patients. Further evidence from real-world studies is needed to confirm the present findings, particularly by inclusion of patient-level clinical information across the different therapeutic areas.

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