Drug survival of the first course of anti-TNF agents in patients with rheumatoid arthritis and seronegative spondyloarthritis: analysis from the MonitorNet database

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Abstract

Objective

To compare drug survival of different anti-TNF drugs (infliximab, INF, etanercept, ETA, and adalimumab, ADA) in rheumatoid arthritis (RA) and spondyloarthritis (SpA) by analysing data collected from an Italian multicentre observational cohort study.

Methods

All patients with RA or SpA registered in the MonitorNet database who started their first course of anti-TNF therapy were included. Overall drug survival was measured, along with specific reasons of discontinuation (inefficacy or adverse events). A first set of analyses using RA as reference category assessed the relationship between diagnosis and drug survival. A second set of analyses stratified by diagnosis (RA and SpA) used INF as reference drug. Adjustment for confounders was performed. The results are presented as adjusted hazard ratios (adjHR) and 95% confidence intervals (95%CI).

Results

2640 RA patients and 1220 SpA patients with a median follow-up of 17 months (IQR 7.2-33.4) were included in the analyses. Patients with a diagnosis of SpA showed a lower risk of drug discontinuation with an adjHR (95%CI) of 0.81 (0.73, 0.90). In SpA, the subset of patients with ankylosing spondylitis (AS) showed the best survival on treatment. In RA, both ETA and ADA showed a significantly lower probability of withdrawal when compared to INF [adjHR (95%CI) 0.46 (0.38, 0.56) and 0.68 (0.57, 0.81), respectively]. Similar results were found in SpA.

Conclusion

Drug survival for SpA is longer than that in RA mainly due to the AS subgroup. In both RA and SpA, ETA and ADA showed a better retention on treatment when compared to INF.

Key words

rheumatoid arthritis, spondylarthropathies, anti-rheumatic agents, pharmacoepidemiology.

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Introduction

Data from national registries on the post-marketing use of biological agents in the treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpA) have provided additional efficacy and safety data when compared with that gathered from clinical trials. These data are important because they relate to real life and not to the controlled setting of randomised controlled clinical trials which typically lack generalisability. Therefore, data from observational studies of heterogeneous groups of patients have allowed further specification of the clinical benefit and long-term toxicity, and thus provided valuable data to the rheumatology community and the health authorities.

Despite the absence of experimental comparisons between anti-TNF agents, indirect analysis of RCTs suggests that efficacy and safety profiles are very similar in the treatment of RA (1). The observational registries, which included large sample sizes and long follow-up timeframes, further clarified the issue by only identifying minor differences in performance between the different anti-TNF agents in clinical practice. While data from long-term use of anti-TNF are already widely available for RA (2-14) less is known on their use in the management of SpA and comparative analysis on anti-TNF effectiveness in the two disease groups has not been yet extensively investigated. The most robust existing evidence comes from the BIOBADASER register in which SpA compared to RA were associated with a better clinical outcome (3). In addition, national Italian data on the comparative effectiveness of different anti-TNF agents for several indications, including SpA, are still lacking.

In this contest, the length of time on a drug (or drug survival) is a reliable tool to assess effectiveness. Drug survival measures the overall benefit of a treatment (effectiveness) that is the result of both positive (persistent efficacy) and negative (loss of efficacy and adverse events) treatment effects, as well as a series of medical and non-medical factors (those not primarily related to the treatment effect) that influence drug use (18). Thus, drug survival has been extensively utilised in pharmacoepidemiological studies on biologics in rheumatic diseases, including RA and SpA (19).

In January 2007, the Italian Society for Rheumatology (SIR) promoted a pharmacoepidemiological study funded by the Italian Regulatory Agency (AIFA) on patients treated with biologic agents and diagnosis of RA, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). All the Italian hospital rheumatology units were invited to participate. In the past 5 years more than 4,000 patients from 27 centres were included in the register. The overall objective of this register was to evaluate and compare biological agents in terms of safety, effectiveness and appropriateness in order to improve patient care and knowledge on these new agents (20).

The aim of this analysis was to investigate the influence of diagnosis and specific anti-TNF agents on drug survival in a convenience sample of patients with RA and SpA recruited across a number of Italian centres and who were receiving their first course of a TNF inhibitor in routine care.

Patients and methods

Patient population

Patient data for this analysis were extracted from the MonitorNet database. MonitorNet is a database established by the SIR in January 2007 and funded by AIFA for the active long-term follow-up of patients with RA and SpA treated with biologic agents. All rheumatology units in Italy were invited to participate in this non-interventional study, and 27 decided to participate. Inclusion criteria were: a) age ≥16 years; b) diagnosis of either RA, PsA or AS; c) moderate-to-severe disease according to the judgment of the treating rheumatologist; d) failure of an adequate therapeutic course with disease-modifying anti-rheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs for AS patients; e) no contraindications to biologic therapy as stated in the summary of product characteristics of each drug.

Baseline and follow-up data

All data were collected from each participating centre through a web-based

case report form. At the start of the anti-TNF treatment, collected data included demographics, current and previous DMARD treatment, comorbidities, rheumatoid factor positivity in RA, disease activity indexes (DAS28 (21) in RA and Bath ankylosing spondylitis disease activity index (BASDAI) (22) in SpA), disease severity indexes (Italian version of the Health Assessment Questionnaire (HAQ) (23) in RA and Bath ankylosing spondylitis functional index (BASFI) (24) in SpA).

The date of any change of anti-TNF therapy, together with the reasons for stopping (inefficacy, adverse events or 'other') the drug were systematically recorded over the follow-up.

Data analysis

MonitorNet data up to April 2012 were used for this analysis. All patients with RA or SpA (PsA or AS) who started their first course of anti-TNF therapy (infliximab, INF; etanercept, ETA; or adalimumab, ADA) and with at least one registered follow-up visit were included in the analysis. The day of the first administration was set as starting date of observation which continued until the last day of treatment or last follow-up visit. Transient treatment interruption (<3 months) was allowed whenever patients restarted the same anti-TNF therapy.

The primary outcome was persistence with the first anti-TNF therapy, defined as the length of time the patients continued to receive their first anti-TNF therapy (25). Specific reasons of discontinuation (inefficacy and adverse events) were explored as secondary outcomes.

Kaplan-Meier estimators were used to describe the persistence with anti-TNF therapy across patients with RA or SpA. The log-rank test was used to compare crude survival between diagnoses. Univariate and multivariate Cox proportional hazard models were used to compare discontinuation rates. The proportional hazard assumption was formally tested based on Shoenfield residuals. In a first set of analyses differences between RA and SpA were analysed using RA as reference category and with estimation of crude hazard ratios (HR) and HR adjusted for age, gender, disease duration, DMARD use, anti-TNF drug and calendar year.

In a second set of analyses the study population was stratified by diagnosis into RA and SpA, and within each subpopulation the influence of specific anti-TNF drugs was investigated. Using the INF category as reference, crude and adjusted HRs were estimated. Prespecified confounders included age, gender, number of comorbidities, disease duration, RF (only for RA), number of previous DMARDs, concurrent DMARDs, baseline disease activity (DAS28 for RA and BASDAI for SpA, respectively) and baseline indexes of functional impairment (HAQ for RA and BASFI for SpA).

Given the high number of adjusting variables, the high probability that a given subject had missing data on at least one variable, and hence be excluded from the adjusted analysis, may have introduced selection bias. To avoid this, multiple imputation was used, with 10 data sets being imputed using chained regression by utilising the 'ice' package in Stata (26).

In all cases three models were developed: (1) any stop, (2) stopping due to inefficacy and (3) discontinuation due to adverse events. The results are presented as HR and 95% confidence intervals(CI). Incident rate of adverse events have been calculated and presented along with exact 95%CI. Stata 11 software was used for all statistical analyses (STATA Corporation, College Station, Texas, USA).

Results

Baseline characteristics

By April 2012, 3860 patients registered with MonitorNet met the inclusion criteria for the current analysis [2640 RA patients, and 1220 SpA patients (722 patients diagnosed with PsA and 498 patients diagnosed with AS)]. All these patients started a first course of anti-TNF therapy at the beginning of the observation time.

Baseline characteristics of the entire cohort stratified by diagnosis and anti-TNF drug are presented in Table I.

Compared with RA patients, patients with SpA were younger, more commonly male, more likely to receive INF and to have less previous and concurrent DMARDs utilisation.

In RA, differences in the baseline characteristics between anti-TNF were found. Patients on INF showed more active disease, worse functional impairment and utilised more DMARDs, both with INF and before starting it.

Differences among different anti-TNF groups were also observed in patients with SpA. Patients receiving INF were younger, more likely to be male, had a longer disease duration and a lower frequency of concurrent use of DMARDs.

Drug survival

Over a median follow-up of 17 months (IQR 7.2–33.4 months), persistence with the first course of TNF treatment was slightly better in SpA than in RA (Table II; Fig. 1), with a crude HR (95%CI) of 0.83 (0.73, 0.94). After controlling for age, gender, disease duration, comorbidities, concurrent DMARD use, TNF drug and calendar year, SpA was still associated with a significantly better survival than that of RA [adjHR (95%CI) 0.81 (0.73, 0.90)].

In the subgroup of SpA, AS showed the lowest discontinuation rate (adjHR [95%CI] 0.59 [0.46, 0.75]), due both to lower discontinuation for inefficacy (adjHR [95%CI] 0.65 [0.47, 0.91]) and adverse events (adjHR [95%CI] 0.50 [0.30, 0.81]). In the adjusted analyses, gender and DMARDs use were associated to worse (adjHR [95%CI] 1.36 [1.18, 1.57]) and better (adjHR [95%CI] 0.74 [0.62, 0.87]) survival on treatment, respectively.

Cohort stratification by diagnosis showed that in the subgroup of RA patients treatment survival was significantly better for ETA and ADA as compared with INF, with an adjHR (95%CI) of 0.46 (0.38, 0.56) and 0.68 (0.57, 0.81), respectively. Similar results were observed when the analysis was carried out against discontinuation for inefficacy or adverse events (Table III).

In the primary analyses on the overall drug survival, ETA showed a marginally better outcome when compared with ADA, while the difference was

Table I. Baseline characteristics.

	RA				SpA			
	INF n=718 (27.2%)	ETA n=1035 (39.2%)	ADA n=887 (33.6%)	All n=2640	INF n=317 (11.7%)	ETA n=543 (55.4%)	ADA n=360 (32.9%)	All SpA n=1220
Age, mean (SD)	54.1 (12.6)	54.3 (13.9)	54.8 (12.2)	54.4 (13.0)	46.9 (12.7)	50.9 (12.7)	48.3 (12.3)	49.1 (12.3)
Gender (female), n (%)	551 (76.7)	829 (80.2)	718 (80.9)	2098 (79.5)	121 (38.2)	244 (44.9)	187 (51.9)	552 (45.2)
Comorbidities, median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Disease duration (years), median (IQR)	6.0 (1.0-12.0)	6.7 (2.3-13.0)	6.1 (1.6-12.1)	6.3 (1.9-12.7)	5.0 (1.3-10.9)	4.3 (1.4-9.9)	3.6 (0.9-8.7)	4.2 (1.2-9.7)
Rheumatoid Factor, n (%)	125 (54.3)	452 (60.6)	323 (55.1)	900 (57.6)	-	-	-	-
Previous DMARDs, median (IQR)	3 (2-3)	2 (1-3)	2 (2-3)	2 (2-3)	1 (1-2)	2 (1-2)	1 (1-2)	1 (1-2)
Concurrent DMARD, n (%)	690 (96.1)	916 (88.5)	818 (91.5)	2418 (91.6)	220 (69.4)	431 (79.4)	298 (82.8)	949 (77.8)
DAS28, mean (SD)	5.6 (1.5)	4.8 (1.6)	4.9 (1.5)	5.1 (1.5)	-	-	-	-
HAQ, median (IQR)	1.5 (1-2)	1.2 (0.9-1.9)	1.2 (0.9-1.6)	1.25 (0.9-1.9)	-	-	-	-
BASDAI, mean (SD)	-	-	-	-	4.8 (2.3)	4.6 (2.3)	4.8 (2.4)	4.7 (2.3)
BASFI, mean (SD)	-	-	-	-	4.8 (2.5)	4.4 (2.4)	4.4 (2.5)	4.5 (2.5)

INF: infliximab; ETA: etanercept; ADA: adalimumab; SD: standard deviation; IQR: interquartile range; DMARD: disease-modifying anti-rheumatic drug; DAS: disease activity score; HAQ: health assessment questionnaire; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index.

Table II. Estimates of drug survival according to diagnosis.

	12 months	24 months	36 months
Rheumatoid arthritis	0.82 (0.80, 0.83)	0.71 (0.69 0.73)	0.62 (0.60, 0.65)
Spondyloarthritis	0.85 (0.82, 0.87)	0.73 (0.69, 0.76)	0.66 (0.62, 0.69)
PsA	0.83 (0.79, 0.86)	0.73 (0.69, 0.77)	0.64 (0.58, 0.69)
AS	0.87 (0.83, 0.89)	0.72 (0.67, 0.77)	0.69 (0.63, 0.74)

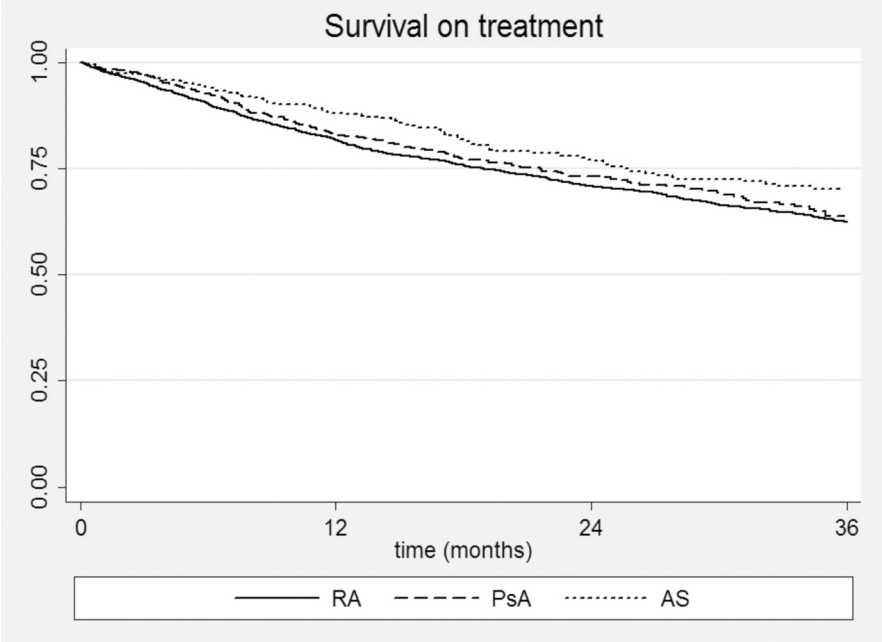

Fig. 1. Kaplan–Meier estimates of crude persistence with anti-TNF by diagnosis. Survival on treatment is statistically better for SpA versus RA (log rank test p=0.005); and within SpA significantly better for AS versus PsA (log rank test p=0.03).

not statistically significant by analysing specific reasons of discontinuation. Analysing the influence of confounders on the overall survival in RA, the following variables were associated with significant difference in risk of discontinuation: concurrent use of DMARD (adjHR[95%CI] 0.59 [0.48, 0.73]) and baseline DAS28 (adjHR[95%CI] 1.09 [1.03, 1.15]).

In the subgroup of patients with diagnosis of SpA, both ETA and ADA showed a significantly better overall survival on treatment than INF with an adjHR (95%CI) of 0.46 (0.33, 0.63) and 0.61 (0.43, 0.85), respectively. When analysing reasons for discontinuation only ETA still showed a lower risk of discontinuation for inefficacy when compared to INF, while the reduction of risk of discontinuation for adverse event was not significantly different for ETA and ADA (Table III). Among fitted confounders with the overall treatment survival in SpA, female gender resulted the major independent predictor of drug discontinuation, adjHR [95%CI] 1.95 [1.54, 2.47]).

An exploratory analysis of the occurrence of specific AEs did not found any significant differences between the different groups of diagnosis and treatment (Table IV).

Table III. Cox proportional hazard estimates (95% CI) for anti-TNF therapy discontinuation for overall and specific reasons stratified by diagnosis.

Diagnosis	Drug	Overall		Ineffectiveness		Adverse events	
		Crude HR (95%CI)	Adjusted HR (95%CI)[§]	Crude HR (95%CI)	Adjusted HR (95%CI)[§]	Crude HR (95%CI)	Adjusted HR (95%CI)[§]
RA	Infliximab	ref	-	-	-	-	-
	Etanercept	0.57 (0.48, 0.67)	0.46 (0.38, 0.56)	0.62 (0.49, 0.77)	0.46 (0.35, 0.59)	0.53 (0.39, 0.71)	0.49 (0.35, 0.69)
	Adalimumab	0.80 (0.68 ,0.94)	0.68 (0.57, 0.81)	0.84 (0.68, 1.04)	0.70 (0.55, 0.89)	0.72 (0.54, 0.96)	0.66 (0.48, 0.91)
SpA	Infliximab	ref	-	-	-	-	-
	Etanercept	0.71 (0.54, 0.92)	0.46 (0.33, 0.63)	0.74 (0.52, 1.06)	0.48 (0.31, 0.75)	0.99 (0.58, 1.68)	0.59 (0.32, 1.11)
	Adalimumab	0.99 (0.75, 1.33)	0.61 (0.43, 0.85)	1.27 (0.86, 1.86)	0.76 (0.48, 1.19)	0.92 (0.50, 1.70)	0.56 (0.28, 1.12)

[§]RA adjusted for age, gender, comorbidities, disease duration, previous DMARDs, RF, concurrent DMARD use, DAS28, HAQ score and calendar year; SpA adjusted for age, gender, diagnosis, comorbidities, disease duration, previous DMARDs, concurrent DMARD use, BASDAI, BASFI and calendar year.

Table IV. Types of adverse events occurring in patients with rheumatoid arthritis and spondylarthritis treated with anti-TNF.

	RA			SpA		
	Infliximab	Etanercept	Adalimumab	Infliximab	Etanercept	Adalimumab
Person-year	1953	1961	1652	540	910	442
Adverse event	IR (95%CI)[§]	IR (95%CI)[§]	IR (95%CI)[§]	IR (95%CI)[§]	IR (95%CI)[§]	IR (95%CI[§]
Reaction	3.1 (1.1, 6.7)	1.5 (0.3, 4.5)	3.6 (1.3, 7.9)	3.7 (0.5, 13.4)	2.2 (0.3, 7.9)	4.5 (0.5, 16.3)
Infection	46.6 (37.6, 57.2)	17.8 (12.4, 24.8)	17.6 (11.8, 25.2)	7.4 (2.0, 18.9)	4.4 (1.2, 11.2)	6.8 (1.4, 19.8)
Cutaneous	3.1 (1.1, 6.7)	9.7 (5.8, 15.1)	10.9 (6.5, 17.2)	3.7 (0.4, 13.4)	3.3 (0.7, 9.6)	4.5 (0.5, 16.3)
Cytopenia	2.0 (0.6, 5.2)	2.0 (0.6, 5.2)	4.2 (1.7, 8.7)	0 (0, 6.8)	1.1 (0.0, 6.1)	0 (0, 8.3)
Neoplastic	0 (0, 1.9)	3.6 (1.4, 7.3)	3.6 (1.3, 7.9)	0 (0, 6.8)	1.1 (0.0, 6.1)	0 (0, 8.3)
Pulmonary	1.5 (0.3, 4.5)	1.0 (0.1, 3.7)	0.6 (0.0, 3.4)	3.7 (0.4, 13.4)	0 (0, 4.0)	2.3 (0.1, 12.6)
Cardiovascular	5.6 (2.8, 10.1)	5.6 (2.8, 10.0)	6.7 (3.3, 11.9)	1.8 (0.0, 10.3)	2.2 (0.3, 7.9)	2.3 (0.1, 12.6)
Endocrine	0 (0, 1.9)	0 (0, 1.9)	0 (0, 2.2)	0 (0, 6.8)	0 (0, 4.0)	0 (0, 8.3)
Gastrointestinal	6.1 (3.2, 10.7)	14.3 (9.5, 20.6)	15.7 (10.3, 23.1)	16.7 (7.6, 31.7)	2.2 (0.3, 7.9)	13.6 (4.9, 29.5)
Ophthalmological	0.5 (0.0, 2.8)	2.0 (0.6, 5.2)	1.8 (0.4, 5.3)	0 (0, 6.8)	1.1 (0.0, 6.1)	0 (0, 8.3)
Psychiatric	0 (0, 1.9)	0 (0, 1.9)	0 (0, 2.2)	0 (0, 6.8)	0 (0, 4.0)	0 (0, 8.3)
Neurological	0 (0, 1.9)	2.0 (0.6, 5.2)	6.7 (3.3, 11.9)	1.8 (0.0, 10.3)	0 (0, 4.0)	4.5 (0.5, 16.3)
Gynecological	1.0 (0.1, 3.7)	0 (0, 1.9)	0 (0, 2.2)	0 (0, 6.8)	1.1 (0.0, 6.1)	4.5 (0.5, 16.3)
Urological	0.5 (0.0, 2.8)	0.5 (0.1, 2.8)	0.6 (0.0, 3.4)	0 (0, 6.8)	0 (0, 4.0)	0 (0, 8.3)
Other	3.6 (1.4, 7.4)	12.2 (7.8, 18.2)	12.7 (7.9, 19.4)	1.8 (0.0, 10.3)	4.4 (1.2, 11.2)	11.3 (3.7, 26.4)

[§]Incident ratio (IR) and exact 95% confidence interval (CI) per 1000 patient-years of exposure.

Discussion

In the present analysis, we compared drug survival on the first course of anti-TNF in a sample of patients with RA and SpA, using data collected from the Italian register MonitorNet.

We found that patient with SpA have a 19% lower probability than patients with RA to discontinue anti-TNF drugs even after adjustment for age, sex, disease duration, comorbidities, concomitant use of DMARDs, anti-TNF drug and calendar year. This difference was mainly due to the AS subgroup of SpA. In general, our results are in line with previous studies that examined the persistence on biological therapies reporting improved drug survival in patients with SpA compared with those with RA. The first study on the subject, published by Carmona and coworkers, reported a 44% reduction in the probability to discontinue the first course with anti-TNF in patients with SpA compared to those with RA, even after adjusting for age, sex, and the use of INF (3). Though no differences between SpA subgroups were found, in the adjusted analyses the PsA subgroup did not longer significantly differ from RA. This result was also reproduced in our study and in the analysis of the NOR-DMARD register carried out by Heiberg and colleagues in which AS but not PsA was significantly associated with longer drug survival than in RA after adjustment for confounders (27). Other indirect evidence of better drug survival in SpA treatment comes from separate analyses of other national registers (11, 16, 17, 25, 28).

The slightly better effectiveness of anti-TNF in SpA might depend on several factors. Different demographical characteristics, disease-specific features, such as younger age at onset and less frequent or less severe age-related comorbidities might account for such better outcome. On the other hand, more frequent use of co-medications, such as methotrexate (MTX) and corticosteroids, might account for the higher risk of discontinuation due to adverse events in RA patients. Nevertheless,

several data indicate that concomitant MTX in RA enhances the efficacy of the anti-TNF agents and positively influences treatment persistence (2, 25). Furthermore, the well-known better response to anti-TNF therapy of inflammatory arthritides with pure axial involvement might account for both the differences between RA and SpA, and that within SpA (3, 27). Also the use of different INF dosages in different SpA subsets of patients might have had a role; in the British register only 22% of patients received the dose of INF licensed for PsA (5 mg/kg), whilst the remaining 78% received the 3 mg/kg dosage as recommended for RA (16). The higher dose of INF recommended for AS seems not to increase the rate of AEs (3). Moreover, the apparent better clinical profile on anti-TNF in SpA might also be due to the lack of valid and effective therapeutic options besides anti-TNF agents, while several other biologic agents targeting other molecules are available in RA.

In the stratified analyses that compared different TNF inhibitors, we found a similar survival on treatment patterns in RA and SpA.

In RA, both ETA and ADA showed a significantly lower probability of discontinuation of treatment than INF for both inefficacy and adverse events. Even after adjusting for confounding factors, there was an average reduction of the probability of drug discontinuation of 54% for ETA and 32% for ADA with a marginal difference in favour of ETA over ADA. This corresponds to results of other observational studies (8, 12, 29, 30).

In our study, in SpA patients we found an improved drug survival for treatment with ETA and ADA compared to INF with a decreased probability of drug discontinuation of 54% and 39% for ETA and ADA, respectively, and no significant difference between the ETA and ADA. Carmona and colleagues have reported a better survival for the first course of ETA in SpA compared with RA although different anti-TNFs in the SpA subgroup were not directly compared (3). A separate evaluation of data on PsA and AS from the Danish register showed no major differences among INF, ADA and ETA in terms of drug survival but only weak trends in favour of ADA and ETA compared to INF (28).

Our study has some limitations. Firstly, it must be acknowledged that this is an observational study and therefore may only suggest associations rather than infer causal relationships. We adjusted for measurable confounders but we could not exclude confounding by unmeasured factors.

This study included a convenience sample of patients who may not be entirely representative of the general population. In addition, the recruitment period of the study compared with the dates of registration of drugs, the therapeutic indication and national recommendations for treatment with biologics have certainly selected a sample with peculiar characteristics compared to the registries of other countries (31-33). Also, treatment decisions and thresholds for stopping treatment might change both over time and between physicians. Subjective opinion of the treating physician might have influenced both the choice of the starting anti-TNF agent and the time of drug stopping. "Inefficacy" as cause of drug discontinuation was differently defined across centres and remains largely physician-dependent. Finally, we did not analyse the causes of transient treatment discontinuation in order to minimise reporting bias. All these limitations may affect external validity of the results.

Comparison between different diseases is debatable because of intrinsic differences in demographic, comorbid conditions, genetic background and pathophysiology of the disease itself which may influence the outcome independently from the pharmacological action of the drugs.

The interpretation of the results on drug survival in terms of effectiveness should be cautious because of several reasons. For example, being INF dosage not taken into account, drug survival might be underestimated in comparisons between drugs. The longer ETA survival with respect to that of the other two anti-TNF agents might depend on factors unrelated to treatment effect which still influence drug use. Calendar year is one of the most important factors. Given that INF was the first anti-TNF to be marketed in Italy, early patients were more likely to start on this drug, being probably those affected by more severe and refractory disease. The bias toward the use of "newer and better" drugs might also have worsened survival on INF. On the other hand, we did not differentiated between lack of response or loss of efficacy, giving more weight to early response rather than long term efficacy, which can be influenced by other factors such as anti-drug antibody production (34).

In conclusion, this study describes drug survival on a first course of anti-TNF therapy in a large cohort of Italian patients with RA and SpA by comparatively evaluating the effectiveness of different drugs for different indications. Drug survival was quantitatively longer for SpA but qualitatively similar in RA and SpA and with greater efficacy with ETA and ADA when compared to that with INF.

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