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Eight-year retention rate of first-line tumor necrosis factor inhibitors in spondyloarthritis: a multi-center retrospective analysis

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Short title: 8-year drug survival of TNFis in SpA

ABSTRACT.

Objective. To evaluate the 8-year survival of the first TNF inhibitor (TNFi) in patients with axial spondyloarthritis (axSpA) or psoriatic arthritis (PsA), identify the predictive factors for withdrawal, and compare the discontinuation rates for infliximab, etanercept, and adalimumab.

Methods. We evaluated PsA and axSpA patients treated with a first-line TNFi between 2005 and 2015 at four Italian tertiary centres. 8-year drug survival was calculated by Kaplan-Meier method and risk for discontinuation among treatment groups compared by stratified log-rank test. Univariate and multivariate Cox proportional hazard models were developed to examine predictors of withdrawal.

Results. Out of 614 patients (316 axSpA, 298 PsA), 203 received adalimumab, 131 etanercept, and 280 infliximab, with similar frequencies in axSpA and PsA subgroups. The cumulative 8-year retention rate in the whole population was 55.1% (57.2 and 51.9% and for axSpA and PsA, respectively; p=NS). No significant differences were observed in drug persistence among individual TNFi in either group. Male sex (HR 0.595, 95% CI 0.405-0.875; p=0.008) and concomitant methotrexate use (HR 0.648, 95% CI 0.426-0.985; p=0.042) were associated with a lower risk of withdrawal in PsA and high baseline BASDAI (HR 0.9842 95% CI 0.9708-0.9980; p=0.028) in axSpA. No difference was found in the comparative analysis of reasons for discontinuation between PsA and axSpA.

Conclusion. We reported that the real-life 8-year retention rate of the first TNFi in axSpA and PsA is over 50%, with no significant differences between axSpA and PsA and irrespective of the individual TNFi.

SIGNIFICANCE AND INNOVATION.

- The 8-year retention rate of first-line TNFi is similar in axSpA and PsA, cumulatively being 55.2%;
- Treatment survival is comparable for etanercept, adalimumab, and infliximab in both PsA and axSpA;
- TNFi treatment persistence was associated with male sex and concomitant methotrexate use in PsA and a high baseline BASDAI in axSpA.

INTRODUCTION.

Spondyloarthropathies (SpA) encompass axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) as the major clinical phenotypes (1). The treatment of SpA changed dramatically with the advent of biologic drugs (bDMARDs), particularly TNFalpha inhibitors (TNFis) (2). Currently, five TNFis (infliximab, adalimumab, etanercept, and more recently golimumab and certolizumab pegol) have been licensed for SpA by the US Food and Drug Administration and the European Medicines Agency. Despite relevant evidence supporting the short-term TNFi efficacy and safety profile in SpA from randomised controlled trials (RCTs) (3,4), data on their long-term effects are limited. Moreover, RCTs external validity may be significantly limited by stringent exclusion and inclusion criteria, thus decreasing the applicability of results to daily clinical practice (5). Because of these issues, large population-based registries are being used in rheumatology to evaluate the long-term performance of bDMARDs in a real life setting, despite the possible lack of the controlled characteristic of RCTs (6).

Drug retention may be considered as a reliable indicator of overall treatment effectiveness in observational studies, as it is mainly determined by both drug efficacy and safety profile. Although many studies from US and European registries have provided abundant data about TNFi drug survival in rheumatoid arthritis (RA), retention rates in SpA are limited to 4 years (7-12). To fill this gap, we performed a retrospective multicentric study and determined the 8-year retention rate of first-line TNFi in a large cohort of real-life patients affected by axSpA and PsA, comparing the between-group withdrawal rates for each TNFi (infliximab, etanercept, and adalimumab) and evaluating the potential predictors of drug discontinuation and reasons for withdrawal due to adverse events.

METHODS.

Data source and patients

We included patients ≥18 years with a diagnosis by treating rheumatologists of axSpA or PsA, who were prescribed a bDMARD between January 2002 and May 2015 in four tertiary rheumatology centres. All patients gave their written informed consent in a single registry approved by the local Ethics Committees. Demographic features (age, sex, and time since axSpA or PsA diagnosis) and therapeutic data (biologic therapy, concomitant sDMARDs and steroids use) were extracted at baseline and every 6 months until the database lock on 31st May, 2015. The analysis was carried out on patients who received infliximab, etanercept or adalimumab as first-line biologic therapy. Moreover, to balance the exposure among the considered biologic drugs, the evaluation was limited to the period when all the three TNFis were available in Italy (from January 2005) as a setting with similar access to each drug. Exclusion criteria were a previous therapy with a biologic agent or the enrollment in a randomized controlled study. Treatments were administered in routine care in accordance with international recommendations: TNFis were prescribed according to licensed regimen and concomitant sDMARDs or corticosteroids were administered if ordered by the referring rheumatologist.

Outcome.

The main outcome was 8-year drug survival, retrospectively calculated as the time period until the definitive treatment interruption or the first missed dose after initiation of TNFi therapy. Discontinuations were considered definitive when indicated in the registry or when no consecutive re-introduction of treatment was reported. All observations were censored at the last registered visit before May 31st, 2015. Patients discontinuing TNFi due to pregnancy or inactive disease/remission were censored at the date of discontinuation and thus not counted as events in

the survival analysis. The reasons for TNFi withdrawal were arrayed into three major categories: inefficacy (primary and secondary lack of response), adverse events (AEs), and others (including remission, desire for pregnancy, and patient preference). Additional drug survival sub-analyses were conducted by stratifying the study population according to diagnosis (axSpA versus PsA) and reasons for TNFi replacement.

Statistical analysis.

Descriptive statistics were used for continuous variables to calculate mean and standard deviation, median and interquartile range. Associations between categorical variables were assessed by chi-square tests. Differences between treatment groups were analysed by the Kruskal-Wallis test. Survival distribution curves were computed by the Kaplan-Meier method and compared by a stratified log-rank test. Univariate and multivariate Cox proportional hazard models were developed to examine potential predictors of TNFi withdrawals. Separate models were used in both PsA and axSpA for overall discontinuation, discontinuation due to adverse events, and discontinuation due to inefficacy (primary and secondary lack of response). Our models included gender, HLA-B27 positivity (for axSpA), TNFi agent, and concurrent use of MTX (for PsA) as categorical variables, whereas age and disease duration at the beginning of TNFi therapy, BASDAI (for axSpA), and Disease Activity Score 28 [DAS-28] (for PsA) as continuous variables. Results are presented as hazard ratios (HRs) with 95% confidence intervals (95% CI). Statistical analyses were performed using SPSS statistical software, version 20.0 (SPSS, Chicago, IL, USA). P values equal to or less than 0.05 were considered statistically significant.

RESULTS.

Baseline characteristics.

Our study cohort (n=614) included 316 patients with axSpA (71.5% ankylosing spondylitis and 28.5% non-radiographic axSpA) and 298 with PsA (4.7% with predominantly axial and 95.3% with peripheral involvement) treated with a first-line TNFI between 2005 and 2015. Enrolled patients received infliximab (101 in PsA and 179 in axSpA group), adalimumab (108 in PsA and 95 in axSpA group), or etanercept (89 in PsA and 42 in axSpA group). The baseline demographic and clinical characteristics of the study population are reported in Table 1. No statistically significant difference was found among the three treatment subgroups for all the considered baseline variables for both axSpA and PsA.

Drug survival.

The cumulative 8-year retention rate in the SpA population was 55.1% (51.9 and 57.2% for PsA and axSpA, respectively) (Figure 1). No significant differences were found in the overall drug survival in PsA compared to axSpA (HR 1.267, 95% CI 0.965 to 1.664; p=0.088). In the PsA subgroup, the estimated proportion of patients maintaining infliximab, adalimumab, and etanercept was respectively 65.82, 62.3, and 76.4% after 3 years, 56.9, 60.4, and 71.6% after 5 years, and 44.9, 51.8, and 65.8% after 8 years. Similarly, in the axSpA subgroup the retention rate of infliximab, adalimumab, and etanercept was respectively 73.4, 78.4, and 83.7% after 3 years, 64%, 76.2, and 79.9% after 5 years, and 50.7, 76.2, and 69.2% after 8 years (Figure 2). No significant differences emerged in the comparison of drug survival among TNFis in both axSpA (p=0.105) and PsA (p=0.142). Infliximab and etanercept showed similar survival rates in PsA and axSpA (HR 1.219, 95% CI 0.846 to 1.755; p=0.288; and HR 1.424, 95% CI 0.669 to 3.033; p=0.359, respectively), whereas adalimumab showed a significantly higher survival in axSpA than in PsA patients (HR 1.810, 95% CI 1.038 to 3.145; p=0.037).

Reasons for discontinuation.

Overall, 266 (43.1%) patients (133 [44.6%] PsA and 133 [42.1%] axSpA), stopped the first-line TNFi. Detailed causes of withdrawal are reported in Table 2. Discontinuation was due to inefficacy in 117 (19.1%) patients (67 [22.4%] PsA and 50 [15.8%] axSpA) and due to AEs in 92 (15%) patients (47 [15.8%] PsA and 45 [14.2%] axSpA). No differences were observed between axSpA and PsA in the risk of drug withdrawal due to inefficacy (HR 1.395, 95% CI 0.967 to 2.013; p=0.075) or AEs (HR 1.123, 95% CI 0.746 to 1.691; p=0.578). (Figure 3)

The sub-analysis of reason for discontinuation according to individual TNFi revealed no significant difference in the frequency of withdrawal because of both inefficacy and AEs in axSpA and PsA subgroups. In particular, etanercept, adalimumab, and infliximab were stopped because of inefficacy in 14.6%, 22.2%, and 29.7% (p=0.055) and because of AEs in 15.7%, 11.1%, and 20.8% (p=0.664) PsA patients. In the axSpA subgroup the frequency of withdrawal for etanercept, adalimumab, and infliximab was 9.5%, 12.6%, and 19% because of inefficacy (p=0.389) and 11.9%, 7.4%, and 18.4% because of AEs (p=0.122).

Predictors of drug survival.

The results from the univariate and multivariate analyses examining predictors of drug discontinuation in axSpA and PsA patients are reported in Table 3. Male sex (HR 0.595, 95% CI 0.405 to 0.875; p=0.008) and concomitant methotrexate use (HR 0.648, 95% CI 0.426 to 0.985; p=0.042) were associated with a lower overall risk of withdrawal only in PsA but not in axSpA. Baseline high BASDAI was a predictor of drug persistence in axSpA in the univariate model although with a minor magnitude (HR 1.016, 95% CI 1.002 to 1.030; p=0.028), whereas high baseline DAS28 was not associated with discontinuation in PsA. Disease duration and age did not predict the persistence on treatment in both PsA and axSpA patients.

DISCUSSION.

We report herein that the long-term retention rates on first-line TNFi in a large cohort of routine care SpA patients, comparing adalimumab, etanercept and infliximab after 8 years is 55.1% (median time-on-drug 110.68 months), with no statistically significant difference in the comparison between PsA (51.9%) and axSpA (57.2%) subgroups or among the individual anti-TNF agents.

To our knowledge, this is the first report evaluating TNFi persistence in a real-life scenario with a prolonged follow-up period, whereas the vast majority of previous similar studies have limited the observation to 3 years. The overall SpA 3-year survival rate in our sample (68%) is consistent with data reported in the Italian cohort Monitornet (66%) (11) and in the Spanish national registry BIOBADASER (10) (74%). Moreover, our short-term drug survival according to disease subgroups (72 and 64% at 3 years for axSpA and PsA, respectively) are comparable to those previously described by other national registries such as the Norwegian NOR-DMARD (77.5 and 77.3% at 1 year) (13), Danish DANBIO (63 and 57% at 2 years) (7,8), the Spanish BIOBADASER (76 and 73% for ankylosing spondylitis [AS] and PsA, respectively, at 3 years) (10), the Italian MonitorNet (69 and 64% at 3 years) (11), the British BSRBR (59% for PsA at 3 years) (9) and an Italian observational cohort (51% for PsA at 4 years) (12). Compared with our 8-year data, previous reports suggested that the overall discontinuation rate of the first TNFi is higher during the first period of treatment and becomes progressively lower after 3 years, probably linked to the progressive positive selection over time of patients presenting a good clinical response without serious AEs. Moreover, specific AEs such as infections have been proven to be more frequent in the first phases of TNFi treatment, with a subsequent decrease for longer treatments (14,15). However, our data are very reassuring in demonstrating the long-term favourable TNFi safety profile for the treatment of SpA

since the discontinuation rate because of AEs in our cohort did not increase over time, with a very low long-term occurrence of more serious AEs such as malignancies and cardiovascular events. Of note, we observed no significant difference in the long-term safety profile of individual anti-TNF agents, showing a similar pattern of withdrawal because of AEs.

The overall retention rate in our SpA cohort was higher compared with similar studies conducted in RA (10,11,13,16), including the one we recently reported in a local population of methotrexate insufficient responder RA patients (34% at 8 years) (17). Albeit this comparison has several limitations, we are convinced that the observed differences may be due to demographical features, disease-specific characteristics, such as younger age at onset and less frequent or less severe age-related comorbidities, different TNFi dosage and concomitant treatment, or the lack of valid and effective alternative options besides TNF blockade in axSpA. No significant differences were found between PsA and axSpA in terms of demographic baseline characteristics and both subgroups included patients with long-standing and severe disease, reflecting the real-life scenario of TNFi prescription for SpA in daily practice. Despite showing a non-significant trend towards a better retention rate in axSpA compared with PsA patients (57.2 versus 52.5% at 8 years), we could not confirm the data by Carmona et al in the BIOBADASER registry (10) and by Brocq et al in a French cohort (16).

Predictive factors associated with TNFi retention rate in SpA are still unclear as no observational study reported an association between drug continuation and disease duration or disease activity at treatment initiation. Younger age has been described as a predictor of TNFi persistence in SpA in the BIOBADASER registry (10) and in AS in the DANBIO registry (7), but not in PsA in both the BSRBR cohort (9) and the DANBIO registry (8). Similarly, baseline high CRP predicted a better drug survival in both AS and PsA patients in the DANBIO (7,8), but not in the BSRBR (9) registry. In our cohort age, disease duration, or baseline CRP do not predict drug withdrawal in both overall SpA

population and individual disease subgroups but baseline disease activity predicts drug retention only in the axSpA subgroup. This latter observation may be the result of the different tools used to define disease activity, since BASDAI in axSpA provides a more accurate measure compared with DAS28 in PsA. Of note, female sex is associated with a lower retention rate in PsA, as previously reported (8,9,13), possibly reflecting the less severe and less rapidly progressing PsA in women (18). Nonetheless, tender joint count and disease activity scores are generally higher in women, mostly due to different pain perception mechanisms or a higher prevalence of fibromyalgia which may contribute to the worse impairment of quality of life and an earlier prescription or stopping of TNFis (19,20). A similar effect of gender in predicting a worse TNFi drug survival has been observed in ankylosing spondylitis from the DANBIO registry (7), whereas in our population female sex is not associated with a higher risk of TNFi discontinuation in axSpA. A possible explanation for that apparent discrepancy may be the longer follow-up period in our analysis compared to the DANBIO registry (8 vs 2 years), as a very recently published prospective study conducted over a 12-year follow-up period in the Outcome in AS International Study (OASIS) cohort had no gender-attributable differences in disease activity, clinical response, or functioning over time (21). The effect of concomitant MTX in improving TNFi drug survival has been recently demonstrated in large cohorts of patients with PsA (22) and axSpA (23). Our analysis confirms these findings only in PsA, whereas the small size of axSpA MTX-treated sample did not allow to find any association.

In the previous experience with the use of TNFi for RA, the majority of reports pointed toward a better retention rate of etanercept compared with monoclonal antibodies (17,24,25). On the contrary, in the present analysis no major differences were observed with the use of infliximab, etanercept and adalimumab. Consistent with previous reports (8), infliximab showed the worse retention rate in both subgroups, but in our cohort this trend was not statistically significant. Moreover, adalimumab persistence was significantly higher in axSpA compared with PsA. These

findings may be explained by considering the frequent coexistence in SpA (especially axSpA) of extra-articular manifestations such as uveitis and inflammatory bowel disease, in which TNFi monoclonal antibodies have been proven to be more effective than etanercept, affecting drug survival.

The main limitation of the present study is its observational retrospective design without randomization. Consequently, patients with a different discontinuation risk could have been channelled to a specific drug, producing selection bias and potentially affecting our comparative analysis. However, we observed that the treatment subgroups are balanced for both axSpA and PsA, with no statistically significant differences in demographic and baseline disease characteristics. Moreover, as usual in long-term drug survival analyses, the number of patients at risk tends to progressively decrease by time becoming relatively small at the end of the evaluated follow-up period, partially influencing the impact of results. On the other side, the most important strength is the very long follow-up period, which allowed for the first time the evaluation of 8-year retention rate and the long-term comparison in the same cohort of TNFi drug persistence in axSpA and PsA patients.

In conclusion, we report that TNFis in PsA and axSpA cohorts are associated with a high long-term retention rate and a good profile of safety. Future analyses in larger population should be advocated to confirm our results.

Legends to figures.

Figure 1: Eight-year overall drug survival on first TNF inhibitor in PsA and axSpA patients.

Figure 2: Eight-year drug survival rates by TNF inhibitor in PsA (A) and axSpA (B) subgroups.

Figure 3: Cumulative incidence of discontinuation for inefficacy (A) and adverse events (B) in PsA and axSpA subgroups.

Table 1: Baseline characteristics of study population according to disease and TNF inhibitor.

[a]Kruskal-Wallis; [b]chi-squared test

ADA, adalimumab; IFX, infliximab; ETN, etanercept; DAS28, disease activity score for 28 joints; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein.

Table 2: Reasons for discontinuation by TNF inhibitor in PsA and axSpA subgroups.

ADA, adalimumab; IFX, infliximab; ETN, etanercept.

Table 3: Predictors of treatment failure in patients with PsA and axSpA treated with TNFi.

ADA, adalimumab; IFX, infliximab; ETN, etanercept; DAS28, disease activity score for 28 joints; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein.

Table 1. Baseline characteristics of study population according to disease and TNF inhibitor.

	PsA					axSpA				
	Total	IFX (n=101)	ADA (n=108)	ETN (n=89)	P value	Total	IFX (n=179)	ADA (n=95)	ETN (n=42)	P value
Mean age, yrs	47.81 (SD 12.14)	46.63 (SD 14.49)	48.92 (SD 11.21)	47.75 (SD 11.67)	0.424[a]	42.84 (SD 12.08)	41.30 (SD 11.91)	44.20 (SD 11.49)	45.40 (SD 13.54)	0.149[a]
Mean disease duration, yrs	8.76 (SD 7.72)	9.31 (SD 7.40)	9.04 (SD 7.78)	7.88 (SD 7.93)	0.142[a]	7.21 (SD 7.95)	7.53 (SD 7.80)	6.77 (SD 8.34)	7.04 (SD 7.71)	0.303[a]
Males (%)	154 (51.67%)	56 (55.44%)	59 (54.62%)	49 (55.05%)	0.993[b]	221 (69.93%)	127 (70.94%)	61 (64.21%)	33 (78.57%)	0.216[b]
Mean DAS28	4.51 (SD 1.5)	4.61 (SD 1.65)	4.39 (SD 1.37)	4.53 (SD 1.5)	0.729[a]	-	-	-	-	-
Mean BASDAI	-	-	-	-	-	4.5 (SD 2.1)	4.9 (SD 2.3)	4.1 (SD 2.3)	4.3 (SD 2.0)	0.074[a]
Mean CRP (mg/dL)	1.53 (SD 1.82)	1.92 (SD 1.93)	1.15 (SD 1.57)	1.5 (SD 1.89)	0.071[a]	1.47 (SD 1.55)	1.62 (SD 1.55)	1.21 (SD 1.51)	1.02 (SD 1.6)	0.166[a]

Table 2. Reasons for discontinuation by TNF inhibitor in PsA and axSpA subgroups

		PsA				axSpA			
		Total	IFX	ADA	ETN	Total	IFX	ADA	ETN
Inefficacy									
	Primary no response	13	1	8	4	7	4	3	0
	Secondary no response	54	29	16	9	43	30	9	4
Adverse events									
	Cutaneous tissue disease	12	2	6	4	4	0	4	0
	Hematologic disease	2	0	0	2	2	1	0	1
	Neuro-psychiatric disease	0	0	0	0	1	0	1	0
	Death	1	0	0	1	1	1	0	0
	Cardiovascular system disease	1	1	0	0	0	0	0	0
	Major infection	3	1	0	2	6	6	0	0
	TB infection	1	1	0	0	1	1	0	0
	Malignancy	6	3	1	2	2	1	0	1

	Infusion/Injection reaction	17	13	2	2	25	23	1	1
	Hepatic toxicity	2	0	2	0	0	0	0	0
	Ocular disease	2	0	1	1	3	0	1	2
Other									
	Lost at follow-up	7	6	0	1	23	17	5	1
	Remission	7	2	3	2	9	6	2	1
	Compliance	2	0	2	0	2	2	0	0
	Pregnancy	3	0	1	2	4	3	1	0
	Total	133	59	42	32	133	95	27	11

Table 3. Predictors of treatment failure in patients with PsA and axSpA treated with TNFi.

		Univariate analysis		Multivariate analysis	
		HR	95% CI	HR	95% CI
PsA					
	Etanercept	1		1	
	Adalimumab	1.5	0.91-2.52	1.6	0.96-2.68
	Infliximab	1.5	0.97-2.48	1.4	0.90-2.34
	Female gender	1.6	1.13-2.37	1.6	1.10-2.42
	Disease duration	0.9	0.95-1.01	0.9	0.95-1.01
	Age	0.9	0.98-1.01	0.9	0.98-1.01
	Baseline DAS28	1.1	0.92-1.35	1.0	0.86-1.31
	Monotherapy	1.5	1.04-2.36	1.5	1.01-2.34
	CRP	1.0	0.89-1.15	1.0	0.87-1.15
axSpA					

Etanercept	1		1	
Adalimumab	1.1	0.53-2.63	1.2	0.54-2.70
Infliximab	1.7	0.89-3.58	1.7	0.87-3.69
Female Gender	1.1	0.77-1.82	1.0	0.68-1.65
Disease duration	1.0	0.97-1.03	1	0.97-1.02
Age	1.0	0.99-1.03	1.0	0.99-1.03
Baseline BASDAI	1.0	1.00-1.03	1.0	0.99-1.02
CRP	1.0	0.95-1.10	1.0	0.93-1.10

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AUTHORS' CONTRIBUTIONS: EGF designed data collection tools, monitored data collection for the whole study, cleaned and analyzed the data, and drafted and revised the paper. He is guarantor. AA, DS, EF, SP, and MM monitored data collection for the whole study. AB wrote and performed the statistical analysis plan, cleaned and analyzed the data, and drafted and revised the paper. MB monitored data collection for the whole study, cleaned and analyzed the data, and drafted and revised the paper. CS, AM, and PLM drafted and revised the paper.

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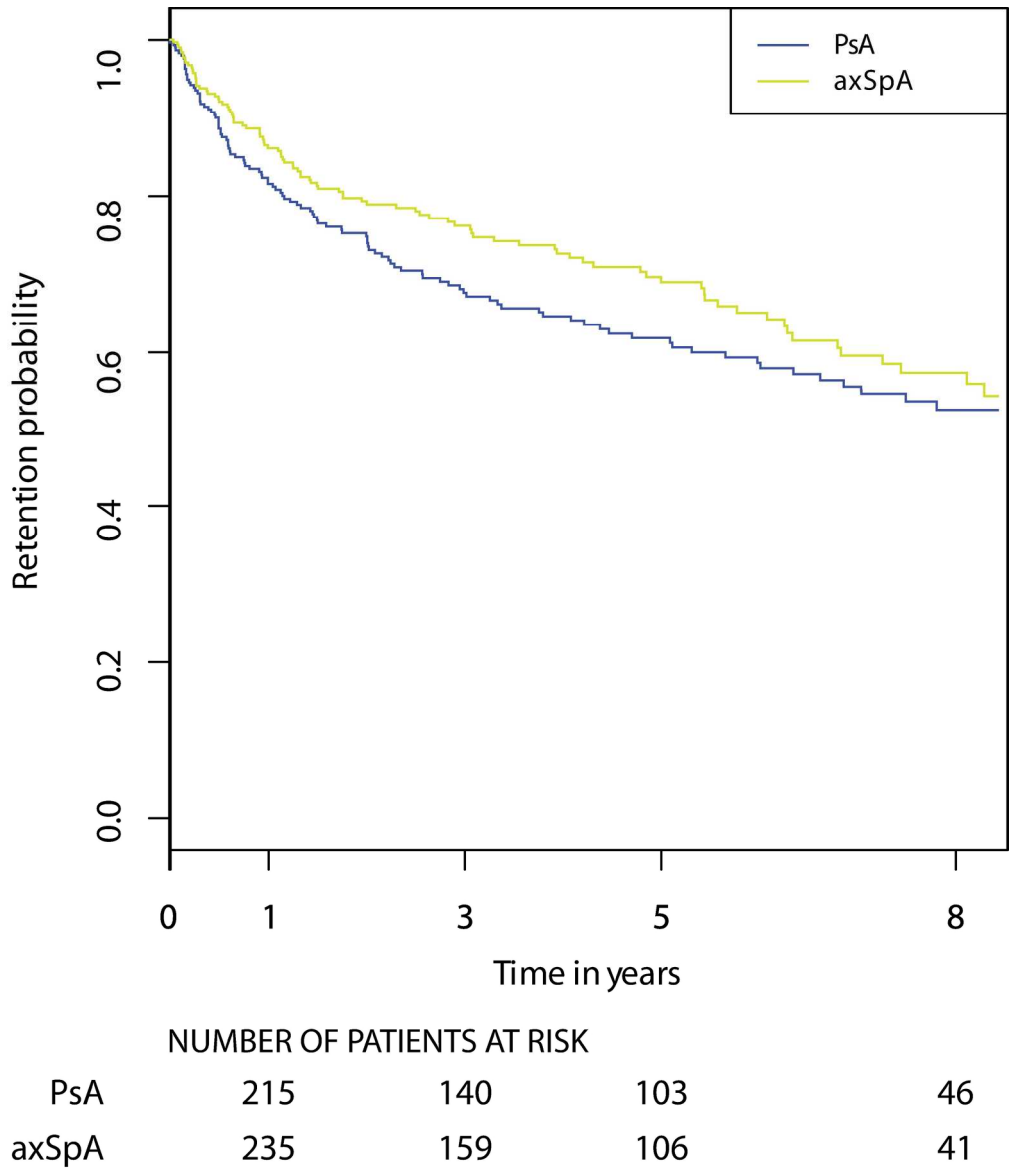

Figure 1: Eight-year overall drug survival on first TNF inhibitor in PsA and axSpA patients.
Figure 1
192x222mm (300 x 300 DPI)

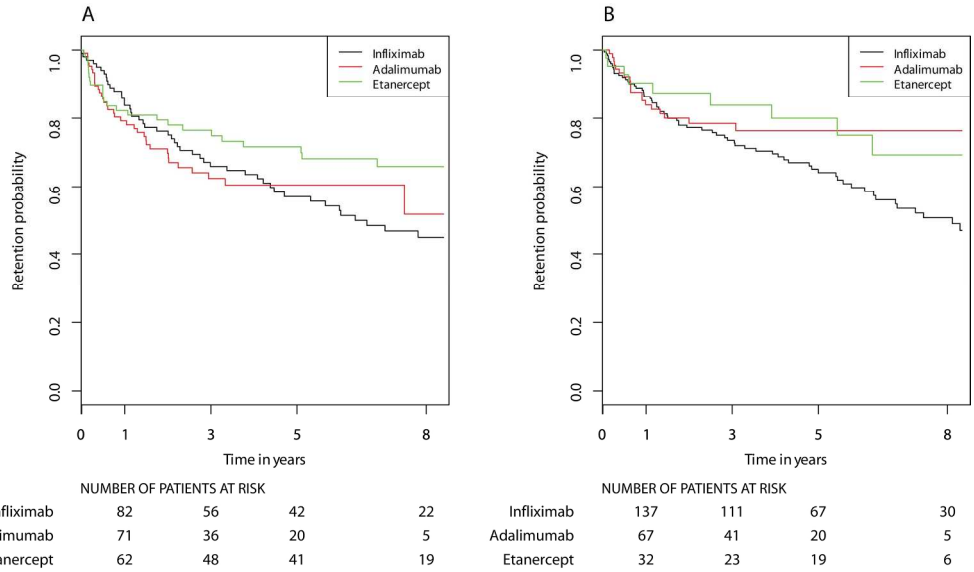

Figure 2: Eight-year drug survival rates by TNF inhibitor in PsA (A) and axSpA (B) subgroups.
Figure 2
213x120mm (300 x 300 DPI)

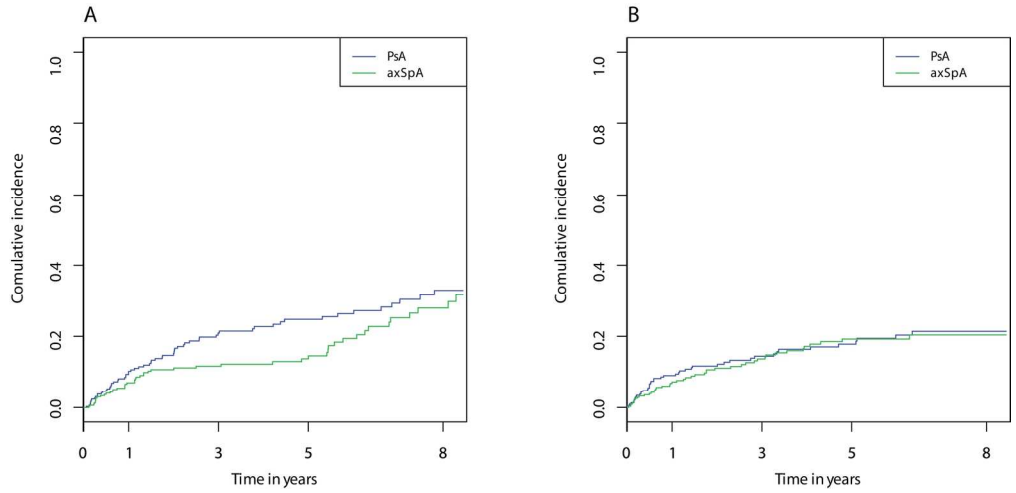

Figure 3: Cumulative incidence of discontinuation for inefficacy (A) and adverse events (B) in PsA and axSpA subgroups.
Figure 3
175x85mm (300 x 300 DPI)