Comparative Analysis and Predictors of 10-year Tumor Necrosis Factor Inhibitors Drug Survival in Patients with Spondyloarthritis: First-year Response Predicts Longterm Drug Persistence

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ABSTRACT. ***Objective.*** To evaluate the 10-year drug survival of the first tumor necrosis factor inhibitor (TNFi) administered to patients with spondyloarthritis (SpA) overall and comparatively between SpA subsets, and to identify predictors of drug retention.

Methods. Patients with SpA in the Hellenic Registry of Biologic Therapies, a prospective multicenter observational cohort, starting their first TNFi between 2004–2014 were analyzed. Kaplan-Meier curves and Cox regression models were used.

Results. Overall, 404 out of 1077 patients (37.5%) discontinued treatment (followup: 4288 patient-yrs). Ten-year drug survival was 49%. In the unadjusted analyses, higher TNFi survival was observed in patients with ankylosing spondylitis (AS) compared to undifferentiated SpA and psoriatic arthritis [PsA; significant beyond the first 2.5 ($p = 0.003$) years and 7 years ($p < 0.001$), respectively], and in patients treated for isolated axial versus peripheral arthritis ($p = 0.001$). In all multivariable analyses, male sex was a predictor for longer TNFi survival. Use of methotrexate (MTX) was a predictor in PsA and in patients with peripheral arthritis. Absence of peripheral arthritis and use of a monoclonal antibody (as opposed to non-antibody TNFi) independently predicted longer TNFi survival in axial disease because of lower rates of inefficacy. Achievement of major responses during the first year in either axial or peripheral arthritis was the strongest predictor of longer therapy retention (HR 0.33, 95% CI 0.26-0.41 for Ankylosing Spondylitis Disease Activity Score inactive disease, and HR 0.35, 95% CI 0.24–0.50 for 28-joint Disease Activity Score remission).

Conclusion. The longterm retention of the first TNFi administered to patients with SpA is high, especially for males with axial disease. The strongest predictor of longterm TNFi survival is a major response within the first year of treatment. (J Rheumatol First Release April 1 2018; doi:10.3899/jrheum.170477)

Key Indexing Terms:
SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS PSORIATIC ARTHRITIS
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Major advances have been made in the pathogenesis, imaging, diagnostic criteria, and classification of spondyloarthritis (SpA)[1,2,3]. Further, treatment of SpA has dramatically changed with the introduction of biologic agents, initially with tumor necrosis factor inhibitors (TNFi), and more recently with interleukin 17 (IL-17) and IL-12/23 blockers. In addition to randomized clinical studies, valuable information to optimize clinical use of these novel and expensive drugs is provided by real-life evidence from registries and cohort studies[4,5,6,7]. However, most of these studies have focused on individual clinical subtypes within the spectrum of SpA, mainly ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Only a limited number of studies, mainly in the early years of TNFi use and with short-term followup, analyzed patients with SpA as a whole group and compared data between subdiagnoses[8,9,10].

Because those diseases represent different types of SpA with many common genetic and pathophysiological characteristics, as well as many overlapping clinical manifestations and similar treatment approaches, we analyzed data from patients with SpA followed by a common protocol in daily practice, to allow for combined as well as comparative analysis. Moreover, reports of short-term therapy outcomes are important but not sufficient regarding the chronic features of SpA. Thus, in our study from the Hellenic Registry of Biologic Therapies (HeRBT), we report on longterm (≤ 10 yrs) followup of patients with SpA starting their first course of TNFi therapy. A comparative analysis was performed of drug adherence and prognostic factors for therapy persistence among patients receiving different TNFi with different clinical subdiagnoses, as well as of axial versus peripheral arthritis.

MATERIALS AND METHODS

Data source. HeRBT is a prospective, observational cohort of patients with inflammatory arthritides receiving biologic therapies in 7 rheumatology academic and nonacademic referral centers throughout Greece (2 in northern, 1 in western, 1 in southern Greece, and 3 in Athens). Until April 2015, nearly 3000 patients had been recruited in the registry. Details about its design and data collection protocol have been published elsewhere[11]. According to the national guidelines, treating rheumatologists are those who decide when a patient has to be treated with a biologic agent. Therapy is fully reimbursed for patients with insurance coverage (the vast majority of the population). According to a recent nationwide study, the prevalence of biologic disease-modifying antirheumatic drug (DMARD) use for arthritis in Greece is 0.19% of the population[12]. Ethical approvals were obtained by local institutional review boards (Heraklion University Hospital decision number 1476) and all participants signed informed consent forms.

Patients (≥ 18 yrs old) with a primary diagnosis of SpA initiating the first TNFi between January 1, 2004, and December 31, 2014, were included. Clinical diagnosis was provided by the treating rheumatologist and was based on former classification criteria since the data register began in 2004. Therefore, patients had either AS, PsA, undifferentiated (u-)SpA, or inflammatory bowel disease (IBD)-related SpA. Only 2 registered patients had a diagnosis of juvenile SpA and 1 patient had reactive arthritis; these patients were excluded. No predefined level of disease activity was required for the patients to be included in the registry, and the choice of TNFi was made by the treating physician. For our present study, patients were followed until discontinuation of the first TNFi, death, loss of followup, or April 30, 2015.

Variables collected. Detailed protocol and variables collected are described elsewhere[11]. In patients with SpA, baseline characteristics additionally included current and/or a history of axial SpA (inflammatory back pain or radiological spondylitis/sacroiliitis) and/or peripheral arthritis (for lower limbs, defined as arthritis distal to the hip) based on the treating clinician's judgment. Thus, patients were characterized at baseline as having isolated axial disease, isolated peripheral arthritis, or combined axial and peripheral arthritis. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were included in cases of axial disease, while 28-joint tender and swollen joint counts and the modified Health Assessment Questionnaire were recorded in cases of peripheral arthritis. Physician global (on a 5-grade Likert scale) and patient global [visual analog scale (VAS) global] assessments and pain (VAS pain) were recorded in all cases. Clinical measures were recorded biannually in the first 2 years and yearly thereafter. Any withdrawal from treatment was registered prospectively and classified by the treating physician as resulting from an adverse event, treatment failure (either primary or secondary), patient decision, pregnancy, disease remission, financial reasons (loss of insurance), or other reasons. In cases of loss of followup of a patient for > 1.5 years, the patient was reported as "lost to followup" at the date of the last recorded followup visit.

Outcome measures. The primary outcome was the 10-year drug adherence (referred to as drug survival) in the whole group, as well as the causes of therapy withdrawal and the predictors for TNFi discontinuation. Secondary outcomes were drug survival according to the 2 major subdiagnoses, and the presence of axial or peripheral arthritis and the relevant predictors. Drug survival was calculated as the time period between the start date [date of the first infusion for infliximab (IFX) and the first prescription of the subcutaneously administered TNFi] and the date of the first missed dose of the drug, death, or April 30, 2015. Temporary treatment interruptions < 6 months (e.g., because of adverse events, surgeries, loss of insurance) were allowed. Discontinuations because of remission of disease (n = 9) were censored at the date of the first missed dose, and patients lost to followup were censored at their last recorded visit.

Statistical analysis. Standard descriptive statistics were applied, and differences between groups were analyzed using the Kruskal–Wallis and chi-square tests as appropriate. Kaplan-Meier plots with log-rank tests, Cox proportional hazards models, and Cox extended models were used to investigate the effect of baseline characteristics and the achievement of a major response within the first year of drug survival. In the regression analyses, information for ≥ 1 covariate was missing in 2–44% of the patients, depending on the analysis. To avoid bias and to increase power, we performed multiple imputations of missing baseline covariate data, while complete-case analyses were also performed. We investigated interactions between sex, TNFi used, clinical diagnosis, ongoing MTX use, and presence of axial or peripheral arthritis. More information on statistical methods and covariates used is available in Supplementary Data 1 (available with the online version of this article). All analyses were performed using the Statistical Package for Social Sciences version 22 (SPSS, SPSS Inc.), and p values of 0.05 (2-tailed) were considered statistically significant.

RESULTS

Patient characteristics. A total of 1077 registered patients

with SpA started treatment with the first TNFi drug, either IFX (61%), etanercept (ETN; 19%), adalimumab (ADA; 17%), or golimumab (GOL; 3.5%; only 1 patient started certolizumab and was not included). Of them, 561 patients had a diagnosis of AS, 375 of PsA, 108 of uSpA, and 33 of IBD-related SpA.

Half of the patients with AS had peripheral arthritis (past or current); nevertheless, it was milder [lower 28-joint Disease Activity Score (DAS28) score] compared to PsA or uSpA patients with peripheral arthritis ($p < 0.001$). On the contrary, BASDAI, BASFI, and Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-reactive protein (CRP) indices were comparable in patients with axial involvement, irrespective of specific diagnoses. Combined axial and peripheral arthritis was reported in 42% of PsA, 57% of uSpA, and 48% of patients with IBD-related SpA. Demographics, disease characteristics, and baseline activity of the whole group and for each subdiagnosis are in Table 1, while data for patients with peripheral arthritis versus those with isolated axial spondylitis are in Supplementary Table 1 (available with the online version of this article).

Therapy discontinuations. Overall, 404 patients (37.5%) discontinued TNFi treatment during a total followup of 4288 patient-years, and 87% of the discontinuations occurred within the first 5 years. Median (IQR) time for discontinuation was 1.6 (0.6–3.1) for AS, 1.4 (0.6–3.1) for PsA, 1.1 (0.5–3.3) for uSpA, and 1.5 (0.4–3.1) years for IBD–related SpA (Table 1 and Figure 1).

Treatment inefficacy was the most frequent cause of discontinuation (43%), followed closely by adverse events (39%). However, for patients with AS, therapy withdrawals were more often because of an adverse event than treatment failure (Table 1). Most prevalent adverse events leading to treatment discontinuation in the whole group were the infusion/injection reactions (71 cases) and psoriatic-like rashes (18 cases), both more common in IFX-treated patients ($p < 0.001$). Other important adverse events leading to TNFi discontinuation included cancer (11 patients), tuberculosis (9 patients), other serious infections (8 patients), and demyelinating disease (4 patients). A summary of the most common adverse events leading to drug discontinuation is given in Supplementary Table 2 (available with the online version of this article).

Unadjusted drug survival analyses. The 5- and 10-year retention rates of the first TNFi therapy in SpA were estimated to be 60% and 49%, respectively. The median (95% CI) estimated time to discontinuation because of failure was 1.57 (1.08–2.05) years while for adverse events and "other reasons" were 1.29 (0.87–1.68) and 2.12 (1.79–2.46) years, respectively (log-rank test, $p = 0.389$; Supplementary Figure 1, available with the online version of this article). In AS, PsA, and uSpA, the estimated 5-year (10-year) drug retention rates were 63% (55%), 59% (42%), and 49% (38%), respectively. Patients with IBD-related SpA had the lowest TNFi drug survival (5-yr: 35%).

The median (95% CI) TNFi survival time in patients with AS was not estimable because > 50% of patients discontinued treatment during followup, while in PsA, uSpA, and IBD-related SpA, TNFi survival time was 7.8 (6.0–9.5), 4.9 (2.0–7.9), and 3.5 (1.6–5.4) years, respectively. Because the survival curves of AS and uSpA crossed at around 2.5 years and those of AS and PsA diverged after about 7 years, 2 separate analyses were performed for each comparison. No significant differences in drug survival were found up to 2.5 and 7 years of followup between patients with AS and uSpA, and AS and PsA, respectively. However, after those timepoints, significant differences were observed (Figure 1A). Of note, patients with AS had significantly lower drug discontinuation rate because of primary failure as compared to patients with uSpA (log-rank test, $p = 0.004$), and because of secondary failure as compared to patients with PsA ($p = 0.030$).

Similarly, a time-dependent association of drug retention according to the specific TNFi used was found. Up to the first 6 months, IFX had the highest retention rate relative to ADA and ETN, with the latter having a comparable survival rate. However, after the first 6 months, ADA was the TNFi best retained, with IFX being intermediate, and ETN having the lowest survival rate (Figure 1B). Selecting for reasons of discontinuation, IFX had significantly fewer stops resulting from primary inefficacy compared to ETN (log-rank test, $p < 0.001$) and ADA ($p < 0.001$), and resulting from secondary inefficacy compared to ETN ($p < 0.001$). In contrast, safety-related drug survival was better with ETN ($p = 0.018$) and ADA ($p = 0.002$) than with IFX. When we selected only patients on IFX, there was a significant difference between accumulation of stops resulting from failure [estimated median time (95% CI): 2.5 (2.04–2.96) yrs] and adverse events [1.5 (0.95–2.04) yrs; log-rank test, $p = 0.025$; Supplementary Figure 2, available with the online version of this article].

Further, overall unadjusted survival rates were higher in men ($p < 0.001$), in patients with baseline CRP > 1.2 mg/dl ($p = 0.005$), and in patients without peripheral arthritis ($p = 0.001$). Patients with isolated axial disease had higher TNFi survival rates compared to both isolated peripheral ($p = 0.017$) and combined peripheral and axial disease ($p = 0.003$; Figure 1C).

Adjusted analyses of drug survival in the whole group. In the multivariable Cox regression analysis, these factors were shown to independently predict longer drug retention in patients with SpA: male sex (HR 0.68, 95% CI 0.55–0.84, $p < 0.001$), use of a monoclonal antibody TNFi versus ETN (HR 0.64, 95% CI 0.50–0.82, $p < 0.001$), MTX co-therapy (HR 0.69, 95% CI 0.55–0.87, $p = 0.001$), and absence of peripheral disease (HR 0.68, 95% CI 0.52–0.88, $p = 0.004$). High baseline CRP had a borderline significance (HR 0.81,

Table 1. Baseline demographics, disease characteristics and activity, and reasons for treatment discontinuation overall and according to clinical subdiagnosis. Values are n (%) or median (IQR) unless otherwise specified.

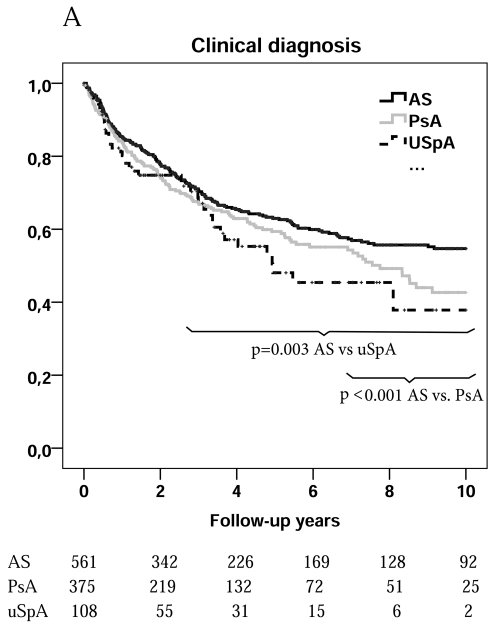
Variables	Valid, n	All, n = 1077	Diagnosis AS, n = 561	PsA, n = 375	uSpA, n = 108	IBD-SpA, n = 33	p‡
Male	1077	711 (66)	446 (80)[c,d,f]	203 (54)[c]	51 (47)[d]	15 (46)[f]	< 0.001
Age, yrs	1077	44 (35–54)	41 (33–50)[c]	49 (39–59)[c,e,g]	41 (33–52)[e]	43 (33–54)[g]	< 0.001
Symptom duration, yrs	1077	9 (3–17)	13 (6–20)[c,d,f]	6 (2–12)[c]	4 (1–11)[d]	6 (2–11)[f]	< 0.001
Symptom duration < 5 yrs	1077	352 (33)	115 (21)[c,d,f]	166 (44)[c]	56 (52)[d]	15 (46)[f]	< 0.001
TNFi							
IFX	1077	655 (61)	382 (68)[c,d]	203 (54)[c]	49 (45)[d]	21 (64)	< 0.001
ETN	1077	200 (19)	81 (14)[c,d]	89 (24)[c,g]	27 (25)[d,h]	3 (9)[g,h]	< 0.001
ADA	1077	184 (17)	87 (16)	64 (17)	24 (22)	9 (27)	0.144
GOL	1077	38 (3.5)	11 (2)[c,d]	19 (5)[c]	8 (7)[d]	0 (0)	0.005
Followup, yrs	1077	2.8 (1.0–5.9)	2.9 (1.0–7.3)[d]	2.8 (1.0–5.4)	2.1 (0.7–4.5)[d]	2.3 (0.9–3.9)	0.024
Axial inflammatory arthritis	913	770 (84)	561 (100)[c,d,f]	121 (53)[c,e,g]	70 (73)[d,e]	22 (76)[f,g]	< 0.001
Peripheral arthritis	944	652 (69)	209 (46)[c,d,f]	336 (94)[c,e,g]	88 (87)[d,e]	22 (76)[f,g]	< 0.001
No. previous csDMARD	1059	1 (0–2)	0 (0–1)[c, d]	1 (1–2)[c,e]	1 (1–2)[d,e]	1 (1–2)	< 0.001
No. co-administered csDMARD	1070	0 (0–1)	0 (0–1)[c,d,f]	1 (1–1)[c]	1 (0–1)[d]	1 (0–1)[f]	< 0.001
Co-administered csDMARD							
MTX	1020	405 (40)	100 (18)[c,d,f]	232 (66)[c,g]	62 (58)[d,h]	11 (36)[f,g,h]	< 0.001
Other	1020	124 (12)	29 (5)[c,d,f]	62 (18)[c,g]	18 (17)[d,h]	13 (42)[f,g,h]	< 0.001
Monotherapy	1070	544 (51)	417 (74)[c,d,f]	86 (23)[c]	32 (30)[d]	12 (36)[f]	< 0.001
Ongoing corticosteroids	1010	115 (11)	24 (5)[c,d,f]	61 (17)[c]	25 (24)[d]	5 (16)[f]	< 0.001
BASDAI, 0–10 [a]	507	5.1 (4.0–6.4)	5.1 (3.8–6.4)	5.2 (4.2–6.2)	5.6 (4.3–7.2)	5.2 (4.1–6.9)	0.303
BASFI, 0–10 [a]	453	5.1 (3.3–6.9)	5.1 (3.2–7.0)	5.1 (3.4–6.9)	5.0 (3.4–6.6)	3.7 (2.6–6.8)	0.891
ASDAS-CRP [a]	440	3.4 (2.8–4.1)	3.5 (2.8–4.1)	3.5 (2.5–4.1)	3.4 (2.4–4.2)	3.4 (3.0–3.8)	0.743
CRP, mg/dl	712	1.2 (0.4–2.7)	1.5 (0.6–3.0)[c,d,f]	1.1 (0.3–2.3)[c]	0.9 (0.3–2.6)[d]	0.6 (0.3–1.1)[f]	0.001
ESR, mm/h	785	30 (16–48)	29 (16–49)	30 (18–48)	25 (13–48)	24 (18–45)	0.545
VAS global, 0–100	796	60 (50–80)	60 (50–80)	65 (50–80)	70 (45–80)	70 (60–80)	0.213
VAS pain, 0–100	760	65 (50–80)	60 (50–80)	70 (50–80)	70 (50–80)	70 (58–80)	0.709
PGA, 0–4	692	3 (2–3)	3 (2–3)[d]	3 (2–3)[e]	3 (3–3)[d,e]	3 (2.8–3)	0.001
Tender joint count[b]	519	3 (1–8)	1 (0–3)[c,d]	5 (2–11)[c,e]	2 (0–5)[d,e]	5 (0–11)	< 0.001
Swollen joint count[b]	519	2 (0–6)	0 (0–1)[c,d,f]	4 (1–8)[c,e]	2 (1–4)[d,e]	2 (0–6)[f]	< 0.001
DAS28-ESR[b]	483	4.5 (3.6–5.4)	3.8 (3.1–4.6)[c,d,f]	5.1 (4.2–6.2)[c,e]	4.4 (3.6–5.3)[d,e]	4.7 (4.0–5.5)[f]	< 0.001
HAQ (0–3)[b]	305	0.8 (0.5–1.3)	0.9 (0.5–1.3)	0.9 (0.5–1.3)	0.6 (0.3–1.1)	0.8 (0.3–1.1)	0.241
Reasons for discontinuation, n (% of stops) [n/100 patients/yr]							
Inefficacy	1077	175 (43) [4.1]	71 (36) [2.9]	70 (47) [5.1]	23 (55) [7.3]	11 (61) [9.8]	
Primary inefficacy	1077	83 (21) [1.9]	34 (17) [1.4]	32 (22) [2.3]	15 (36) [4.7]	2 (11) [1.8]	
Secondary inefficacy	1077	92 (23) [2.2]	37 (19) [1.5]	38 (26) [2.8]	8 (19) [2.5]	9 (50) [8.0]	
Adverse events	1077	159 (39) [3.7]	90 (46) [3.6]	53 (36) [3.9]	11 (26) [3.5]	5 (28) [4.5]	
Other	1077	70 (17) [1.6]	34 (17) [1.4]	26 (18) [1.9]	8 (19) [2.5]	2 (11) [1.8]	
Total	1077	404 [9.4]	195 [7.8]	149 [10.9]	42 [13.3]	18 [16.1]	

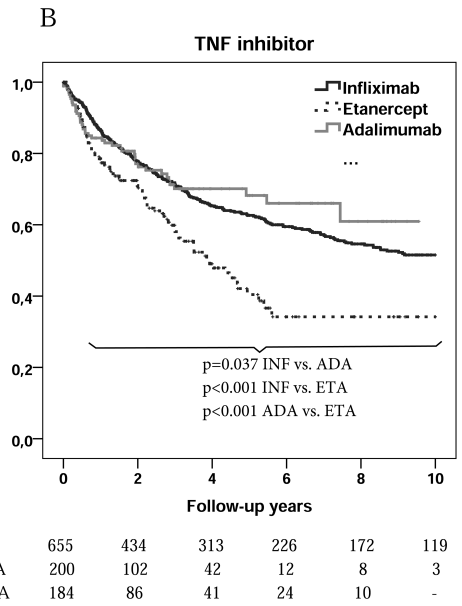
‡p values are determined by chi-square test or Kruskal-Wallis test as appropriate. [a] In patients with axial involvement. [b] In patients with peripheral involvement. P values are for the comparison between the following patients: [c] $p < 0.05$ for AS and PsA; [d] $p < 0.05$ for AS and uSpA; [e] $p < 0.05$ for PsA and uSpA; [f] $p < 0.05$ for AS and IBD-related SpA. [g] $p < 0.05$ for PsA and IBD-related SpA; [h] $p < 0.05$ for uSpA and IBD-related SpA. Several patients in subgroups had missing baseline data for some variables. TNFi: tumor necrosis factor inhibitor; IFX: infliximab; ETN: etanercept; ADA: adalimumab; GOL: golimumab; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score using C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analog scale; PGA: physician's global assessment; DAS28-ESR: 28-joint Disease Activity Score using ESR; HAQ: Health Assessment Questionnaire; AS: ankylosing spondylitis; PsA: psoriatic arthritis; uSpA: undifferentiated spondyloarthritis; IBD: inflammatory bowel disease; IQR: interquartile range.

95% CI 0.64–1.03, p = 0.087; Table 2). Significant interactions regarding TNFi survival were found for the effect of MTX co-therapy according to patient sex and the presence of axial disease. MTX co-therapy was only protective against treatment terminations in men (p = 0.002) and in patients with isolated peripheral disease (p = 0.006). Further, monoclonal TNFi had a better survival rate than ETN in AS (p < 0.001) and uSpA (p = 0.002), but not in patients with PsA (p = 0.576).

Significant predictors for better efficacy-related survival were male sex; use of IFX versus ETN, ADA, and GOL; no peripheral arthritis involvement; and baseline VAS global ≤ 60 mm (Table 2). Similarly, better safety-related survival was predicted by male sex, MTX co-therapy, use of ETN and ADA versus IFX, and prior use of ≥ 1 conventional synthetic (cs-) DMARD.

Prediction of drug survival in AS and PsA. In patients with AS,





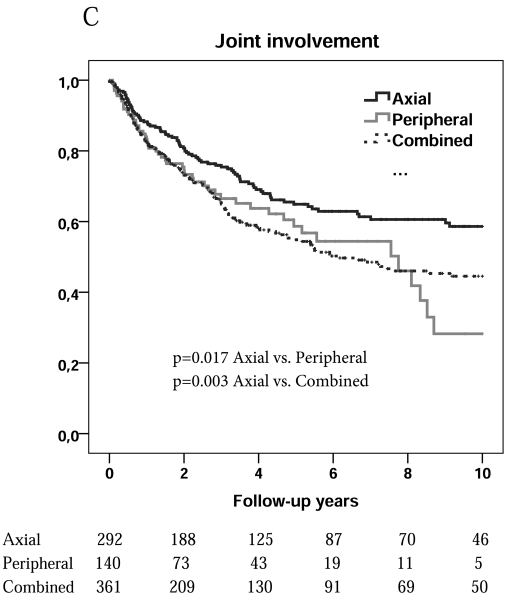


Figure 1. Crude drug survival curves stratified according to diagnosis, TNFi agent used, and joint involvement phenotype. Results are from Kaplan-Meier analyses and log-rank test. In (A) and (B), significant differences were observed between AS and PsA, and AS and uSpA during the periods 7-10 years and 2.5-10 years, respectively, as well as between IFX and ETN, ADA and ETN, and IFX and ADA from 6 months to 10 years. These results were verified in Cox extended analyses and the interactions with time as described were significant, except for HR of discontinuation of ETN versus IFX, which was stable over time. C. Patients with isolated axial disease had higher TNFi survival rates compared to both isolated peripheral and combined peripheral and axial disease. The number of patients still receiving therapy at different timepoints is shown below the graphs. TNFi: tumor necrosis factor inhibitor; AS: ankylosing spondylitis; PsA: psoriatic arthritis; uSpA: undifferentiated spondyloarthritis; INF and IFX: infliximab; ETA and ETN: etanercept; ADA: adalimumab.

therapy with ETN versus a monoclonal antibody, the presence of peripheral disease, and a most recent calendar year (2012–2014) of TNFi initiation independently predicted therapy discontinuation, while the use of csDMARD prior to TNFi start predicted longer drug survival. A trend for male sex predicting higher survival was observed (p = 0.082; Table 3).

Accordingly, in patients with PsA, male sex and co-therapy with MTX were the significant predictors of longer overall TNFi survival (Table 3).

Prediction of drug survival according to the pattern of arthritis: association of first-year responses to TNFi survival. We further sought to assess whether a major first-year response may predict longterm TNFi survival in patients with SpA. To perform this analysis and because of different response indices for different phenotypes, patients were grouped as having axial or peripheral disease at baseline. Univariable and multivariable analyses for baseline predictors of TNFi retention in patients having axial or peripheral arthritis are described in Table 4 and Table 5.

Among patients with axial disease who had complete datasets for assessing BASDAI 50% response (BASDAI50; n = 354) and ASDAS–inactive disease (-ID) state (n = 403),

Table 2. Cox regression analysis for TNFi discontinuation in the whole group of patients with SpA, stratified by reason for discontinuation. Values are HR (95% CI).

Variables	All Reasons		Inefficacy		Adverse Events	
	Univariate	Final Model after Backward Selection	Univariate	Final Model after Backward Selection	Univariate	Final Model after Backward Selection
Sex, male vs female	0.63 (0.52–0.77)[c]	0.68 (0.55–0.84)[c]	0.45 (0.34–0.61)[c]	0.60 (0.44–0.82)[b]	0.79 (0.57–1.11)**	0.57 (0.40–0.81)[b]
Age, per 10 yrs	1.01 (0.93–1.09)		1.04 (0.92–1.17)		1.00 (0.73–1.38)	
Symptom duration, < vs ≥ 5 yrs	1.20 (0.97–1.48)*		1.41 (1.03–1.92)[a]		0.95 (0.67–1.35)	
TNFi agent						
ETN vs other	1.65 (1.30–2.10)[c]	1.56 (1.22–1.99)[c]				
IFX, ref			1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
ETN			3.16 (2.21–4.51)[c]	2.67 (1.86–3.84)[c]	0.52 (0.31–0.90)[a]	0.52 (0.30–0.89)[a]
ADA			1.89 (1.23–2.90)[b]	1.74 (1.13–2.68)[a]	0.38 (0.20–0.73)[b]	0.34 (0.18–0.64)[b]
GOL			4.38 (2.17–8.81)[c]	3.53 (1.74–7.18)[c]	0.25 (0.04–1.78)**	0.24 (0.04–1.69)**
Clinical diagnosis						
AS vs other	0.77 (0.63–0.94)[a]					
AS, ref			1.00 (ref)		1.00 (ref)	
PsA			1.55 (1.10–2.16)[a]		0.93 (0.66–1.32)	
Other			2.31 (1.53–3.48)[c]		0.85 (0.50–1.45)	
Year of TNFi therapy start, per 2 yrs	1.12 (1.04–1.20)[b]		1.30 (1.17–1.44)[c]		0.89 (0.79–1.01)*	
Previous csDMARD, yes vs no	0.96 (0.78–1.17)		1.88 (1.33–2.66)[c]		0.61 (0.44–0.85)[b]	0.68 (0.47–0.99)[a]
MTX co-therapy, yes vs no	0.84 (0.68–1.04)*	0.69 (0.55–0.87)[b]	1.18 (0.86–1.62)		0.55 (0.38–0.79)[b]	0.60 (0.39–0.91)[a]
Axial disease, yes vs no	0.86 (0.65–1.16)		0.65 (0.44–0.97)[a]		1.15 (0.65–2.04)	
Peripheral disease, yes vs no	1.44 (1.13–1.83)[b]	1.47 (1.14–1.91)[b]	2.25 (1.49–3.38)[c]	1.91 (1.25–2.90)[b]	0.90 (0.63–1.29)	
CRP, > vs ≤ 1.2 mg/dl	0.78 (0.62–0.99)[a]	0.81 (0.64–1.03)*	0.80 (0.57–1.13)		0.81 (0.56–1.18)	
VAS global, > vs ≤ 60	1.16 (0.92–1.46)		1.64 (1.15–2.34)[b]	1.47 (1.03–2.10)[a]	0.91 (0.64–1.30)	
PGA, > vs ≤ 2	1.03 (0.81–1.30)		1.13 (0.72–1.77)		0.87 (0.61–1.26)	

* p < 0.1. ** p < 0.2. [a] p < 0.05. [b] p < 0.01. [c] p < 0.001. TNFi: tumor necrosis factor inhibitor; SpA: spondyloarthritis; IFX: infliximab; ETN: etanercept; ADA: adalimumab; GOL: golimumab; AS: ankylosing spondylitis; PsA: psoriatic arthritis; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; CRP: C-reactive protein; VAS: visual analog scale; PGA: physician's global assessment.

59% and 42% achieved BASDAI50 or ASDAS-ID, respectively, at least once within the first year of therapy. After adjusting for baseline variables, a state of ASDAS-ID or a BASDAI50 response within the first year was the strongest predictor of longer TNFi survival (HR 0.33, 95% CI 0.26–0.41, p < 0.001 and HR 0.49, 95% CI 0.34–0.71, p < 0.001, respectively; Table 4).

Accordingly, in patients with peripheral arthritis, DAS28 remission state [evaluable patients: 448 (68%)], the European League Against Rheumatism–good response [EULAR-good; 374 (57%)] and the American College of Rheumatology 70% response [ACR70; 390 (60%)] were achieved by 55%, 58%, and 20% of the patients, respectively, ≥ 1 time within the first year of therapy. In the multivariable model adjusting for baseline variables and DAS28-remission in the first year, this was again the strongest predictor of longer TNFi retention (HR 0.35, 95% CI 0.24–0.50, p < 0.001). Similar results were obtained when adding EULAR-good or ACR70 response to the model (Table 5).

DISCUSSION

Individual diseases of the SpA spectrum share common genetic, pathophysiological, and clinical characteristics. In this context, we consider it important to report for the first time (to our knowledge) combined, longterm, real-life data, registered prospectively with a common protocol for the SpA group of patients. In this analysis of Greek patients with SpA starting their first course of TNFi therapy, a rather favorable drug survival of 60% and 49% at 5 and 10 years, respectively, was found. Among the different baseline variables assessed, having a diagnosis of AS and limited axial phenotype predicted longer drug adherence. Most interestingly, the strongest independent predictor for longterm drug survival was achievement of a major response in axial or peripheral disease during the first year.

To our knowledge, ours are the only available data for 10-year TNFi retention in a prospective observational setting in patients with SpA. Carmona, *et al*[8] analyzed patients with SpA as a group, albeit for a shorter followup time, and

Table 3. Cox regression analysis for TNFi discontinuation stratified by diagnosis. Values are HR (95% CI).

Variables	AS		PsA	
	Univariate	Final Model after Backward Selection	Univariate	Final Model after Backward Selection
Sex, male vs female	0.66 (0.48–0.93)[a]	0.73 (0.51–1.04)*	0.64 (0.46–0.88)[b]	0.62 (0.45–0.86)[b]
Age, per 10 yrs	0.94 (0.74–1.32)		0.91 (0.64–1.29)	
Symptom duration, < vs ≥ 5 yrs	1.40 (1.00–1.97)*		0.90 (0.65–1.26)	
TNFi agent used, ETN vs other	2.17 (1.50–3.15)[c]	1.77 (1.19–2.63)[b]		
TNFi agent used				
IFX, ref			1.00 (ref)	
ETN			1.22 (0.81–1.83)	
ADA			1.25 (0.75–2.06)	
GOL			2.35 (1.12–4.91)[a]	
Year of TNFi therapy start, per 2 yrs	1.24 (1.11–1.38)[c]	1.17 (1.04–1.31)[a]	1.04 (0.92–1.18)	
Previous csDMARD, yes vs no	0.72 (0.53–0.99)[a]	0.65 (0.47–0.90)[b]	1.06 (0.65–1.74)	
MTX co-therapy, yes vs no	0.89 (0.62–1.30)		0.65 (0.46–0.92)[a]	0.61 (0.43–0.87)[b]
Axial disease, yes vs no			0.91 (0.60–1.37)	
Peripheral disease, yes vs no	1.41 (1.02–1.94)[a]	1.53 (1.11–2.10)[b]	1.98 (0.82–4.76)**	2.20 (0.90–5.34)*
CRP, > vs ≤ 1.2 mg/dl	0.83 (0.58–1.19)		0.74 (0.49–1.11)**	
VAS global, > vs ≤ 60	1.15 (0.82–1.63)		1.09 (0.76–1.56)	
PGA, > vs ≤ 2	1.07 (0.73–1.58)		1.06 (0.71–1.58)	
BASDAI, > vs ≤ 5	1.07 (0.74–1.53)			
BASFI, > vs ≤ 5	1.27 (0.84–1.94)			
SJC-28, > vs ≤ 2			1.05 (0.72–1.52)	
TJC-28, > vs ≤ 3			1.24 (0.84–1.84)	
DAS28-ESR baseline, > vs ≤ 4.5			1.06 (0.70–1.62)	

* p < 0.1. **: p < 0.2. [a] p < 0.05. [b] p < 0.01. [c] p < 0.001. TNFi: tumor necrosis factor inhibitor; AS: ankylosing spondylitis; PsA: psoriatic arthritis; IFX: infliximab; ETN: etanercept; ADA: adalimumab; GOL: golimumab; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; CRP: C-reactive protein; VAS: visual analog scale; PGA: physician's global assessment; BASDAI: Bath Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; SJC-28: swollen joint count in 28 joints; TJC-28: tender joint count in 28 joints; DAS28-ESR: 28-joint Disease Activity Score in 28 joints using erythrocyte sedimentation rate.

Table 4. Cox regression analysis for predictors of TNFi discontinuation in patients with axial inflammatory arthritis. Values are HR (95% CI).

Variables	Univariable	Final Model, Adjusted		
		Baseline Variables Only	Baseline Variables and First-year BASDAI50 Response	Baseline Variables and First-year ASDAS-ID Response
Sex, male vs female	0.67 (0.52–0.87)[b]	0.74 (0.56–0.98)[a]	0.62 (0.40–0.95)[a]	0.66 (0.43–1.02)*
Age, per 10 yrs	0.92 (0.73–1.17)			
Symptom duration, < vs ≥ 5 years	1.40 (1.08–1.82)[a]			
TNFi agent used, ETN vs other	1.94 (1.44–2.61)[c]	1.68 (1.24–2.28)[b]		1.88 (1.40–2.53)[a]
Clinical diagnosis				
AS (ref)	1.00 (ref)			
PsA	1.06 (0.76–1.48)			
Other	1.52 (1.09–2.14)[a]			
Year of TNFi therapy start, per 2 yrs	1.20 (1.10–1.31)[c]	1.13 (1.03–1.24)[a]		
Previous csDMARD, yes vs no	0.84 (0.66–1.07)**	0.68 (0.52–0.88)[b]	0.64 (0.42–0.96)[a]	0.71 (0.48–1.05)*
MTX co-therapy, yes vs no	0.96 (0.73–1.25)			
Peripheral disease, yes vs no	1.41 (1.08–1.84)[a]	1.47 (1.12–1.93)[b]		
CRP, > vs ≤ 1.2 mg/dl	0.72 (0.54–0.96)[b]			
VAS global, > vs ≤ 60	1.15 (0.88–1.53)			
PGA, > vs ≤ 2	0.87 (0.64–1.19)			
BASDAI, > vs ≤ 5	1.09 (0.81–1.48)			
BASFI, > vs ≤ 5	1.15 (0.83–1.59)			
BASDAI50, yes vs no	0.49 (0.34–0.72)[c]		0.49 (0.34–0.71)[c]	
ASDAS-ID, yes vs no	0.33 (0.22–0.51)[c]			0.33 (0.26–0.41)[c]

* p < 0.1. ** p < 0.2. [a] p < 0.05. [b] p < 0.01. [c] p < 0.001. TNFi: tumor necrosis factor inhibitor; BASDAI50: 50% improvement of Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-ID: Ankylosing Spondylitis Disease Activity Score–Inactive Disease; ETN: etanercept; AS: ankylosing spondylitis; PsA: psoriatic arthritis; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; CRP: C-reactive protein; VAS: visual analog scale; PGA: physician's global assessment; BASFI: Bath Ankylosing Spondylitis Functional Index.

Table 5. Cox regression analysis for predictors of TNFi discontinuation in patients with peripheral arthritis. Values are HR (95% CI).

Variables	Univariable	Multivariable Model, Adjusting for Baseline Variables Only	Baseline Variables and First-year DAS28 Remission	Final Model, Adjusted Baseline Variables and First-year EULAR Good Response	Baseline Variables and First-year ACR70 Response
Sex, male vs female	0.60 (0.47–0.76)[c]	0.63 (0.49–0.81)[c]			0.74 (0.52–1.06)*
Age, per 10 yrs	0.90 (0.70–1.15)				
Symptom duration, < vs ≥ 5 yrs	1.10 (0.86–1.41)				
TNFi agent used, ETN vs other	1.53 (1.15–2.03)[b]	1.45 (1.09–1.93)[a]	1.92 (1.21–3.04)[b]	1.62 (1.05–2.50)[a]	1.65 (1.06–2.56)[a]
Clinical diagnosis					
AS, ref	1.00 (ref)				
PsA	1.06 (0.81–1.38)				
Other	1.21 (0.84–1.73)				
Year of TNFi therapy start, per 2 yrs	1.08 (1.00–1.17)*				
Previous csDMARD, yes vs no	0.95 (0.72–1.26)				
MTX co-therapy, yes vs no	0.72 (0.56–0.92)[b]	0.65 (0.51–0.84)[b]		0.73 (0.50–1.05)*	0.65 (0.46–0.93)[a]
Axial disease, yes vs no	0.97 (0.72–1.29)				
CRP, > vs ≤ 1.2 mg/dl	0.74 (0.55–0.99)[a]	0.76 (0.57–1.02)*			
VAS global, > vs ≤ 60	1.28 (0.98–1.67)*				
PGA, > vs ≤ 2	1.00 (0.73–1.37)				
SJC-28, > vs ≤ 2	1.26 (0.96–1.66)**				
TJC-28, > vs ≤ 3	1.32 (1.00–1.74)[a]	1.32 (1.00–1.75)*	1.84 (1.10–3.06)[a]	1.82 (1.26–2.62)[b]	1.81 (1.26–2.59)[b]
DAS28 baseline, > vs ≤ 4.5	1.10 (0.84–1.46)		0.61 (0.36–1.03)*		
DAS28 remission, yes vs no	0.39 (0.29–0.55)[c]		0.35 (0.24–0.50)[c]		
EULAR good response, yes vs no	0.42 (0.30–0.60)[c]			0.41 (0.29–0.58)[c]	
ACR70, yes vs no	0.33 (0.19–0.60)[c]				0.29 (0.21–0.40)[c]

* p < 0.1. ** p < 0.2. [a] p < 0.05. [b] p < 0.01. [c] p < 0.001. TNFi: tumor necrosis factor inhibitor; ETN: etanercept; AS: ankylosing spondylitis; PsA: psoriatic arthritis; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; CRP: C-reactive protein; VAS: visual analog scale; PGA: physician's global assessment; SJC-28: swollen joint count in 28 joints; TJC-28: tender joint count in 28 joints; DAS28: 28-joint Disease Activity Score; EULAR: European League Against Rheumatism; ACR70: American College of Rheumatology criteria 70% improvement.

reported a 3-year TNFi survival of 74%, while in a retrospective study, the 8-year survival in axial SpA and PsA patients was 55.1%[13]. Both were rather comparable to our results (3-year = 69% and 8-year = 52%).

A crude comparative analysis of TNFi survival between individual SpA subtypes showed a time-dependent association, with ultimately higher retention rates in AS versus uSpA and PsA patients. This was verified in unadjusted models and adjusted for baseline covariates Cox-extended models (data not shown). Accordingly, Lie, *et al* showed a higher retention rate in AS compared to uSpA[10], similar to our data. However, in other studies of significantly shorter followup, a comparable TNFi drug survival was found between patients with PsA and AS[8,9,13]. These discrepancies could possibly be attributed to different study populations as well as to varying physician therapy withdrawal criteria.

An interesting finding of our analysis was that the absence of peripheral arthritis was an independent predictor of longer drug survival in the whole SpA group, as well as in patients with AS, and this was because of less chance of inefficacy withdrawals. Concerning the effect of peripheral involvement on TNFi retention, data are sparse. Kristensen, *et al* reported that peripheral disease was shown to predict more favorable TNFi retention in AS at 2 years of followup[14]. Shorter followup and other factors may be implicated in this difference and more studies are necessary, especially with the growing group of patients classified as peripheral SpA becoming more clinically significant.

Male sex predicted higher treatment retention both for efficacy and safety reasons, an effect repeatedly shown in both AS and PsA patient studies[5,15], while use of MTX was protective against discontinuations resulting from adverse events. Concerning the effect of csDMARD, the only study for patients with SpA (excluding PsA) from the Rheumatic Diseases Portuguese Register reported no protective effect[16]. Because the effect of csDMARD is dependent on both the disease and individual TNFi agent, differences in these variables among different cohorts may explain observed discrepancies. Along with other studies[5], we found no protective effect of MTX co-medication in AS; this finding is supported by smaller studies[17,18]. On the contrary, investigators from the Antirheumatic Therapies In Sweden registry reported a positive effect of MTX[10]. Although not strongly supported by the evidence thus far and not proposed for the treatment of axial disease by ASAS/EULAR recommendations[19], a favorable effect of MTX, especially for those with peripheral arthritis, cannot be excluded. Concerning PsA, we and others have found a favorable effect of MTX co-administration[15,20], while a report from the COnsortium of Rheumatology Researchers Of North America US-based registry found no effect[21]. A systematic literature review showed that the use of MTX prolongs TNFi

drug survival of monoclonal TNFi[22], and this also supports our findings.

We have previously shown that first-year responses strongly predicted longterm drug survival of TNFi in patients with RA[11]. Early clinical improvements were shown to predict 1- or 5-year clinical responses in patients with SpA, albeit in the context of TNFi clinical trials[23,24]. Interestingly, major response rates within the first year in our present cohort were high and comparable to those in previous studies[5,15,25,26]. To our knowledge, we are the first to report that clinical variables quantifiable early in the treatment course, such as ASDAS-CRP inactive disease state and DAS28-remission state, could predict a 2- to 3.5-fold higher chance of 10-year drug survival in everyday clinical practice.

Our study has certain limitations. We had no data on extraarticular activity (enthesitis, dactylitis, psoriasis, or IBD-related relapses), which may have influenced physicians' treatment decisions. Nevertheless, we may generally assume that "stop failure" was assigned to possible activity relating to these manifestations. Moreover, patients were recruited based on the diagnosis of expert treating rheumatologists and not on classification criteria. This could be considered an inherent limitation of most registries, wherein, comparable to our study, patients are included based on treating rheumatologists' diagnoses[10,15,27,28]. Nevertheless, we have to note that most of our patients had established, longstanding diseases; they were all followed by experienced rheumatologists, and baseline demographics and disease characteristics are well in accordance with available epidemiologic data and those reported by other registries[14,29,30].

Patient body mass index (BMI) and comorbidities such as smoking, which may also interfere with drug survival or responses, were not consistently reported and thus were not included in our main multivariate analyses. Subanalysis in patients with available data on BMI [n = 312, median (IQR) = 26.3 (23.9–29.6)] showed that higher BMI was associated with a lower chance to achieve BASDAI50 and EULAR-good response within the first year in patients with axial and peripheral involvement, respectively. However, other response indices (ASDAS-ID, DAS28-inactive state, and ACR70) were not found to be associated with BMI (data not shown). Regarding smoking, conflicting available data exist in the literature, supporting either a negative effect or no role in drug survival[16,27]. In our cohort, both in univariate and multivariable regression analyses of available data (n = 234, 55% current, 12% past smokers, 33% never smoked), smoking status (treated either as ever/never or as non/past/current smoking) was not a significant predictor for TNFi survival overall (data not shown). Nevertheless, these results should be considered with caution because of the limited data available.

Missing data is another concern in observational studies. We tried to address this by performing multiple imputations of the missing values. Complete-case analyses were also performed, and the results were comparable to that of the imputed data (Supplementary Tables 3-6, available with the online version of this article).

We report a rather favorable 5- and 10-year TNFi survival rate in patients with SpA. Patients with AS showed a higher drug retention rate compared to PsA and uSpA patients. When first-year clinical responses for axial or peripheral disease were included in the multivariate models of drug survival, they were the strongest independent predictors. We thus support close disease activity monitoring as a valuable tool to predict longterm outcomes.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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