

Longterm Clinical Outcomes in 420 Patients with Psoriatic Arthritis Taking Anti-tumor Necrosis Factor Drugs in Real-world Settings

Florenzo Iannone, Simona Lopriore, Romano Bucci, Giuseppe Lopalco, Angela Chialà, Luca Cantarini, and Giovanni Lapadula

ABSTRACT. Objective. An observational study to evaluate the longterm clinical outcomes of adalimumab (ADA), etanercept (ETN), and infliximab (IFX) in patients with psoriatic arthritis (PsA), in real-world settings. **Methods.** From a prospective cohort we studied 420 biologic-naïve patients with PsA who had peripheral arthritis and were beginning a treatment with ADA, ETN, or IFX. Drug survival was evaluated by Kaplan-Meier life analysis, and baseline predictors of drug discontinuation were assessed by Cox regression analysis. The frequency of concomitant glucocorticoids and the daily mean dosage were compared by chi-square test and ANOVA repeated measures across 4 years. **Results.** After 4 years the overall survival of the first anti-tumor necrosis factor- α (anti-TNF) was 51.0%, but significantly higher for ETN (58.9%) than ADA (43.9%) or IFX (44.0%; $p = 0.003$). Patients taking ETN also had the lowest HR of drug discontinuation (HR 0.57, 95% CI 0.34–0.93, $p = 0.02$). The strongest predictor of drug interruption was female sex (HR 2.02, 95% CI 1.28–3.20, $p = 0.002$). The disease duration was inversely correlated with drug discontinuation (HR 0.96, 95% CI 0.93–0.99, $p = 0.02$). The average daily dose of prednisone significantly decreased from baseline: 5.6 ± 2.5 to 4.7 ± 1.9 at 1 year ($p = 0.01$) to 4.0 ± 1.8 at 4 years ($p = 0.001$). Additionally, compared to baseline (49.6%), a significant reduction of patients taking glucocorticoids was detected at 2 years (36.5%, $p < 0.05$), 3 years (29.9%, $p < 0.01$), and 4 years (22.6%, $p < 0.01$). **Conclusion.** In real-world settings, TNF inhibitors showed a high rate of drug survival at 4 years. Further, the need for glucocorticoids for controlling active PsA was lowered with time. (J Rheumatol First Release March 15 2016; doi:10.3899/jrheum.151042)

Key Indexing Terms:

DISEASE ACTIVITY
ETANERCEPT

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The introduction of anti-tumor necrosis factor- α (anti-TNF) drugs is considered a milestone in the treatment of active psoriatic arthritis (PsA), as recommended by international

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guidelines¹, based on several randomized clinical trials (RCT) that have given evidence of the drugs' efficacy and short-term safety^{2,3,4,5,6}. In real-world settings, a widespread surrogate measure of clinical outcomes of anti-TNF treatment is drug survival, a result of drug safety, effectiveness, and patient adherence to therapy. The longer the time of followup, the more informative the data analysis will be. Therefore, more robust data are available for the first TNF inhibitors launched on the market: adalimumab (ADA), etanercept (ETN), and infliximab (IFX). The longest observation time has been reported by the Danish registry DANBIO, in which 764 patients with PsA treated with TNF inhibitors were monitored up to 8 years⁷. No difference was detected among ADA, ETN, and IFX in drug survival, and male sex and higher CRP level were associated with longer drug survival⁷. In the Southern Sweden Arthritis Treatment Group (SSATG) registry, no significant difference among treatments was found, although ETN had half the risk of discontinuing therapy in comparison to IFX⁸. Nevertheless, a 5-year observational study of a small cohort of patients with active PsA found equal effectiveness with ADA, ETN, and IFX, but ETN showed the highest rate of drug persistence⁹.

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The evaluation of drug survival together with the analysis of predictors thereof may also give interesting information about the behavior of clinicians in the management of PsA, such as the administration of concomitant glucocorticoids or disease-modifying antirheumatic drugs (DMARD). However, while in RCT data on concomitant therapies are carefully gathered, in the real world data are usually available at baseline but often lacking during followup. Thus, we usually miss data on the possible effect of anti-TNF agents on use and dosage of glucocorticoids over time. The primary objective of our study was to estimate the 4-year survival of ADA, ETN, and IFX in biologic-naïve patients with PsA. Further, we aimed to evaluate changes in the proportion of patients taking concomitant glucocorticoids and the average daily dose across 4 years of followup.

MATERIALS AND METHODS

Patients. We analyzed data from PsA patients within a longitudinal cohort study followed up at the outpatient rheumatology clinics of Bari, Foggia, and Siena belonging to the Gruppo Italiano Studio Early Arthritis (GISEA) registry. GISEA was launched in 2003 to record and monitor patients with rheumatoid arthritis, PsA, and spondyloarthritis who are treated with biological drugs on the basis of the standard of clinical care. The local Ethics Committee approved the GISEA registry (Trial registry no. NCT01543594), and prior written informed consent to take part was obtained from all patients, in compliance with the Helsinki declaration.

Patient data are recorded at baseline and every 6 months thereafter. The collected data include age, sex, disease duration, the intake of glucocorticoids and DMARD, 68 tender joint count (TJC), 66 swollen joint count (SJC), 28-joint Disease Activity Scores (DAS28), skin involvement by Psoriasis Area and Severity Index (PASI), C-reactive protein (CRP ml/dl), the first-hour erythrocyte sedimentation rate, rheumatoid factor, pain assessed by means of visual analog scale (VAS 0–100), Health Assessment Questionnaire (HAQ 0–3), patient's global assessment of disease activity (PtGA 0–100), side effects, and biological drug discontinuation.

For the purpose of our study, in the period 2003–2013 we consecutively analyzed 420 PsA patients with peripheral articular disease commencing their first ever anti-TNF treatment with ADA, ETN, or IFX. Inclusion criteria were (1) the presence of peripheral PsA, which was diagnosed according to the CASPAR (CIAssification criteria for Psoriatic ARthritis) criteria¹⁰ (oligoarticular or polyarticular subset were defined using a cutoff ≥ 5 involved joints); (2) active disease, defined as DAS28 ≥ 3.2 , and ≥ 3 swollen and tender joints^{11,12}; and (3) failure of at least 2 DMARD among methotrexate (MTX) 15 mg/week, sulfasalazine 2 g/day, cyclosporine 3 mg/kg/day, leflunomide 20 mg/day for 3 months. Exclusion criteria were (1) axial involvement, diagnosed on the basis of inflammatory low back pain and sacroiliitis on imaging, according to the modified New York criteria for the diagnosis of ankylosing spondylitis; and (2) patients previously treated with a first course of anti-TNF drugs. Patients with axial disease, not enrolled in this study and excluded from the analysis, accounted for roughly 10% of our overall PsA cohort.

Patients were prescribed TNF inhibitors according to the rheumatologist's expert opinion at the doses recommended in the official guidelines: ADA 40 mg subcutaneously every other week, ETN 50 mg subcutaneously per week, and IFX 5 mg/kg intravenously at weeks 0, 2, and 6, and every 8 weeks thereafter.

Outcome measures. The primary clinical outcome was the drug survival rate at 4 years and the assessment of baseline predictors thereof. Secondary outcomes investigated across 4 years were the proportion of patients taking the anti-TNF drug as monotherapy and reduction glucocorticoid intake, if any, and the clinical response evaluated as the achievement of a "good"

European League Against Rheumatism (EULAR) clinical response (defined as a DAS28 change from baseline ≥ 1.2 ¹³), an improvement of functional ability considered as a reduction of the HAQ score (Δ HAQ) ≥ 0.5 , and the reduction of the mean number of 66-TJC, 68-SJC, VAS pain, and PtGA from baseline.

Statistical analysis. The Kolmogorov-Smirnov test was used to check a normal distribution of continuous variables. Continuous variables were reported as means and SD if normally distributed, while medians and range were calculated for not normally distributed continuous variables. For categorical variables, counts and percentages were calculated. Differences between groups for normally distributed continuous variables were compared by ANOVA, and the Kruskal-Wallis test was used to compare not normally distributed continuous variables. Within-group comparisons between baseline and each followup time interval were evaluated by ANOVA repeated measures and posthoc Bonferroni test. Differences in the distribution of frequencies were assessed by chi-squared test. Survival of therapy was computed using the Kaplan-Meier life table method, and the log-rank test was used to compare discontinuation rates. Patients contributed to the survival models until the first discontinuation or censoring at 4 years of treatment. Patients stopping anti-TNF because of remission were right censored. The search for a possible predictor of drug discontinuation was performed by univariate and multivariate Cox regression analysis. In the multivariate model, HR of drug discontinuation were adjusted for anti-TNF drug, calendar year, age, sex, disease duration, use of glucocorticoids and DMARD at entry, baseline CRP (≤ 1 mg/dl vs > 1 mg/dl), 68-TJC, 66-SJC, HAQ, and oligo/polyarticular disease. Missing data were not replaced. Analyses were made using the SPSS (version 20) statistical software (IBM), and a p value of < 0.05 was considered statistically significant.

RESULTS

Baseline features. We analyzed data of 420 anti-TNF drug-naïve patients with peripheral PsA [257 females (61%)], who were beginning their first ever treatment with ADA (n = 139), ETN (n = 197), or IFX (n = 84; Table 1). There were no significant differences in age, duration of disease, sex distribution, HAQ, 68-TJC, 66-SJC, or VAS pain among the 3 arms of treatment. However, patients with PsA who were taking IFX had more active disease; DAS28 and PASI were significantly higher among them than in those taking ADA or ETN.

Drug survival and predictors. Crude drug survival curves were evaluated by Kaplan-Meier analysis. The overall retention rate at 4 years was 51.0% (n = 214) in the whole PsA cohort and the mean survival time (MST) was 36.8 months (95% CI 34.8–37.8). The survival rates at 4 years of each treatment group were 58.9% for ETN (MST 38.9, 95% CI 37.0–40.8 months), 44.0% for IFX (MST 36.2, 95% CI 32.9–39.4 months), and 43.9% for ADA (MST 32.7, 95% CI 29.9–35.5 months), and the difference was statistically significant (log rank test, p = 0.003; Figure 1). Cox regression analysis was used to compute estimated HR of drug discontinuation at 4 years, adjusting for calendar year, sex, age, TNF inhibitor, HAQ, CRP ≥ 1 mg/dl, TJC, SJC, glucocorticoid intake, DMARD co-therapy, and oligo/polyarticular disease (Table 2). The strongest predictor of drug interruption was female sex (HR 2.02, 95% CI 1.28–3.20, p = 0.002). Nevertheless, disease duration at entry negatively predicted drug discontinuation (HR 0.96, 95% CI 0.93–0.99, p = 0.02). Considering IFX as a reference, patients taking ETN had

Table 1. Baseline demographics of 420 patients with PsA, subdivided by anti-TNF drug. All data are median (range) unless otherwise indicated.

	All, n = 420	ADA, n = 139	ETN, n = 197	IFX, n = 84	p
Age, yrs	50 (16–81)	46 (18–72)	51 (16–81)	50 (16–77)	0.24
Duration, yrs	4 (0.8–39)	3.3 (0.8–37)	3.0 (0.3–35)	4.5 (0.4–39)	0.32
ESR, mm/h	16 (2–97)	13 (2–90)	16 (2–97)	22 (2–90)	0.03
CRP, mg/dl	0.4 (0.1–14)	0.3 (0.1–12)	0.4 (0.1–14)	0.5 (0.1–10)	0.04
68-TJC	7 (1–59)	7 (1–57)	7 (1–59)	8 (1–47)	0.70
66-SJC	1 (0–42)	1 (0–42)	1 (1–36)	2 (1–33)	0.84
DAS28	4.3 (1.4–8.6)	4.1 (1.4–7.1)	4.2 (1.6–8.6)	4.8 (1.8–8.4)	0.02
HAQ	1.12 (0.1–3.0)	1.12 (0.1–2.75)	1.12 (0.1–3.0)	1.25 (0.1–3.0)	0.81
VAS-Pain	70 (10–100)	60 (10–100)	70 (10–100)	70 (10–100)	0.55
PtGA	70 (10–100)	60 (10–100)	70 (10–100)	70 (10–100)	0.06
PASI	1.2 (0–47)	1.2 (0–47)	0.8 (0–18)	6.3 (0–14)	0.01
Predn (mg/day)	5.0 (2.5–25)	5.0 (2.5–10)	5.0 (2.5–15)	5.0 (2.5–25)	0.08
Female, n (%)	257 (61)	85 (61)	122 (62)	50 (60)	0.91
CRP > 1, n (%)	110 (29)	28 (23)	53 (28)	29 (37)	0.14
Predn, n (%)	204 (50)	67 (50)	102 (52)	35 (43)	0.38
DMARD, n (%)	245 (60)	87 (64)	106 (54)	52 (64)	0.11

PsA: psoriatic arthritis; TNF: tumor necrosis factor; ADA: adalimumab; ETN: etanercept; IFX: infliximab; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; 68-TJC: 68 joint tender joint count; 66-SJC: 66 joint swollen joint count; VAS: visual analog scale; HAQ: Health Assessment Questionnaire; PtGA: patient's global assessment of disease activity; PASI: Psoriasis Area and Severity Index; DMARD: disease-modifying antirheumatic drugs; Predn: prednisone.

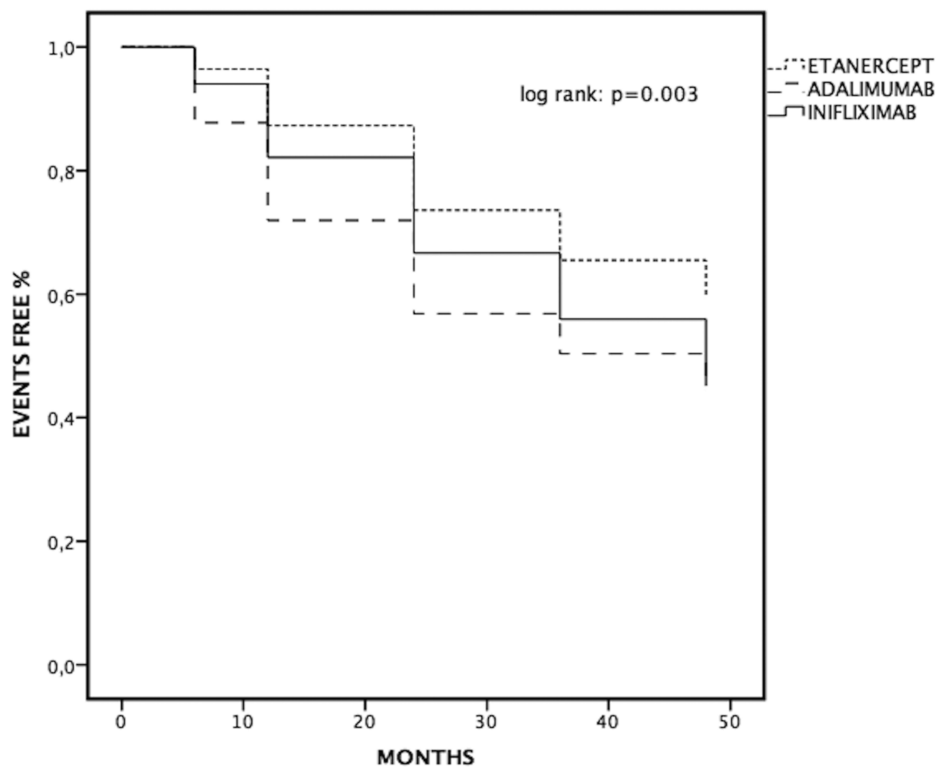


Figure 1. Four-year crude retention rates of anti-TNF therapy in patients with PsA by drug. TNF: tumor necrosis factor; PsA: psoriatic arthritis.

around 40% less HR of drug withdrawal (HR 0.57, 95% CI 0.34–0.93, $p = 0.02$).

Clinical outcomes. Outcomes of anti-TNF therapy were assessed after 6 months, 12 months, and every year thereafter.

Table 2. HR estimates of anti-TNF discontinuation at 4 years by univariate and multivariate Cox regression analysis.

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Baseline covariates						
Age	0.99	0.98–1.00	0.79	0.99	0.98–1.01	0.88
Sex, female/male	1.75	1.20–2.36	0.001	2.02	1.28–3.20	0.002
Disease duration	0.97	0.94–1.00	0.64	0.96	0.93–0.99	0.02
Oligo/polyarticular	0.78	0.58–1.05	0.11	1.20	0.73–1.99	0.45
CRP, ≥ 1 mg/dl / < 1 mg/dl	0.93	0.67–1.29	0.67	1.29	0.83–1.89	0.25
68-tender joint count	1.01	1.00–1.02	0.04	1.00	0.98–1.02	0.71
66-swollen joint count	1.00	0.97–1.03	0.74	0.99	0.95–1.03	0.75
HAQ	1.20	0.97–1.48	0.79	1.16	0.85–1.59	0.32
Calendar year	1.02	0.97–1.07	0.36	1.06	0.99–1.13	0.94
DMARD, yes/no	1.03	0.77–1.38	0.80	0.89	0.61–1.30	0.65
Prednisone, yes/no	1.00	0.76–1.33	0.96	1.08	0.74–1.58	0.65
Drug						
Infliximab	1					
Adalimumab	1.10	0.77–1.58	0.58	0.93	0.56–1.54	0.79
Etanercept	0.68	0.48–0.98	0.04	0.57	0.34–0.93	0.02

TNF: tumor necrosis factor; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug.

A secondary endpoint of the study was evaluation of the intake of glucocorticoids over time, as either daily dosage or percentage of patients, and changes in the concomitant therapy with DMARD. At baseline, the average daily dose of prednisone was 5.6 ± 2.5 , and it progressively decreased to 5.2 ± 2.4 at 6 months, 4.7 ± 1.9 at 1 year ($p = 0.01$), $4.6 \pm$

1.9 at 2 years ($p = 0.01$), 4.6 ± 2.0 at 3 years ($p = 0.01$), and 4.0 ± 1.8 at 4 years ($p = 0.001$). Additionally, a gradual reduction of percentage of patients taking prednisone or DMARD in combination with anti-TNF drugs was seen with time (Figure 2). Compared to baseline (49.6%), a significantly lower percentage of patients taking glucocorticoids

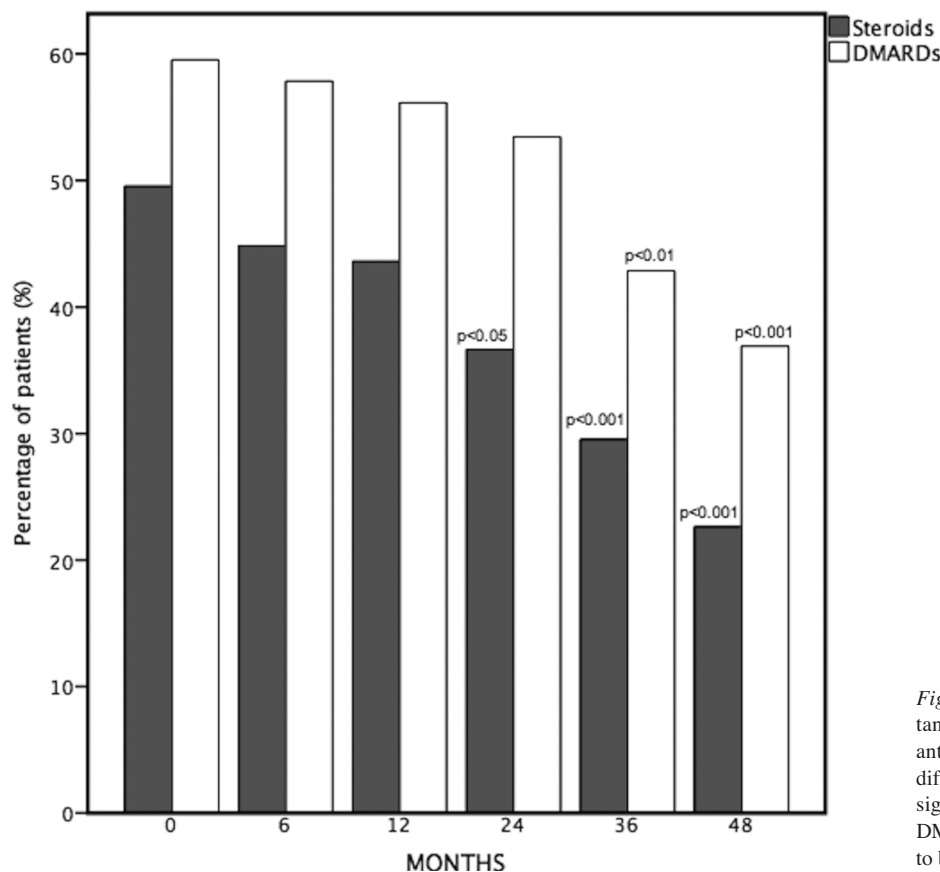


Figure 2. Percentages of patients taking concomitant prednisone (steroids) or disease-modifying antirheumatic drugs (DMARD) at baseline and at different subsequent timepoints. After 24 months, a significant reduction of glucocorticoid and DMARD intake was observed (p values are referred to baseline).

was detected at 2 years (36.5%, $p < 0.05$), 3 years (29.9%, $p < 0.001$), and 4 years (22.6%, $p < 0.001$). Likewise, the percentage of patients taking co-therapy with DMARD was 59.6% at entry, 43.1% ($p < 0.01$) at 3 years, and 36.9% ($p < 0.001$) at 4 years.

Because of the baseline differences among anti-TNF treatments, we studied the percentage of patients achieving an improvement of the DAS28 score ≥ 1.2 ("good" EULAR response) from baseline, and the percentage of patients showing a reduction of the HAQ score (Δ HAQ) ≥ 0.5 . As shown in Table 3, the percentage of patients attaining a "good" EULAR response was significantly higher in IFX at 3 and 4 years of followup. However, the frequency of PsA patients with meaningful improvement of functional ability was not statistically different (Δ HAQ; ≥ 0.5) among treatments, except for IFX at 1 year.

We also assessed the effect of anti-TNF therapy on 68-TJC, 66-SJC, HAQ, and DAS28 (Figure 3A), and VAS-pain and PtGA (Figure 3B) in the whole PsA cohort over time. VAS-pain significantly dropped from 62.2 ± 24 at entry to 23.4 ± 28 at 6 months ($p = 0.001$) and remained steady up to 4 years (21.9 ± 27 , $p = 0.001$). Likewise, PtGA significantly decreased from 66.7 ± 25 at entry to 23.9 ± 28 at 6 months ($p = 0.001$) and further declined until 4 years (22.6 ± 27 , $p = 0.001$). Also the mean of 68-TJC dropped from 10.3 ± 10 at entry to 2.4 ± 5.2 at 6 months ($p = 0.001$) and 1.5 ± 3.8 at 4 years ($p = 0.001$). Additionally, the number of 66-SJC was 2.7 ± 4.6 at baseline, significantly reduced at 6 months (0.26 ± 0.7 , $p = 0.001$), and at 4 years (0.16 ± 0.6 , $p = 0.001$). Baseline HAQ was 1.1 ± 0.6 , 0.37 ± 0.6 at 6 months, and 0.44 ± 0.6 at 4 years ($p = 0.001$). At entry, DAS28 was 4.4 ± 1.3 , 2.2 ± 1.2 at 6 months, and 2.2 ± 1.0 at 4 years ($p = 0.001$).

Anti-TNF therapy was globally safe and well tolerated. Adverse events that led to treatment discontinuation occurred in 48 patients (11.4%). The most frequent ($n = 13$) was rash at the site of injection, followed by infusion reaction ($n = 5$) and flare of skin psoriasis ($n = 3$).

Table 3. Clinical outcomes of anti-TNF treatment up to 4 years in patients with psoriatic arthritis. Frequencies of patients achieving a "good" EULAR response or HAQ improvement ≥ 0.5 from baseline (Δ HAQ) are given. Adalimumab (ADA), etanercept (ETN), and infliximab (IFX) are compared by chi-squared test. Except for p values, data are percentages.

	"Good" EULAR Response				Δ HAQ ≥ 0.5			
	ADA	ETN	IFX	p	ADA	ETN	IFX	p
6 mos	59	70	71	0.13	49	57	46	0.12
1 yr	59	73	78	0.02	55	65	75	0.04
2 yrs	70	74	85	0.17	63	66	69	0.75
3 yrs	67	76	85	0.04	58	62	57	0.62
4 yrs	61	79	83	0.04	61	56	61	0.79

TNF: tumor necrosis factor; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire.

DISCUSSION

The aim of our study was to estimate the 4-year retention of the anti-TNF drugs ADA, ETN, and IFX, in biologic-naive patients with peripheral PsA. We previously reported the 2-year data showing that ETN had the longest survival in polyarticular peripheral PsA¹⁴. Here, we extended the observation to 4 years and assessed the changes in glucocorticoid usage over time. We analyzed 420 patients with PsA and the overall drug persistence at 4 years was 48%, very close to that reported by the regional biologics registry of the SSATG⁸. The Norway registry NOR-DMARD reported a crude retention rate of 57% at 3 years¹⁵, and the Danish registry DANBIO reported the same rate of drug survival (57%) but at 2 years⁷. Obviously, the former is a mere list of rates that cannot be compared because several confounding factors made our cohorts quite different. Unlike the NOR-DMARD¹⁵ or DANBIO⁷ study, in our analysis ETN showed a significantly higher survival at 4 years. But in a small cohort of 65 patients with PsA from Greece⁹, the ETN survival rate was the highest at 5 years followup. Nevertheless, in the study from SSATG, 8 patients with PsA starting ETN showed about half of the hazard of stopping the therapy compared to IFX. Similarly, in our appraisal patients taking ETN had 40% less likelihood than those taking IFX to discontinue the treatment at 4 years. The only other covariate strongly correlating with drug interruption was female sex, as in DANBIO⁷ or in the British Society for Rheumatology Biologics Register¹⁶. We did not find correlations between drug survival and CRP levels or DMARD comedication, as reported^{7,8,17}. More recently, a French survey has shown comorbid cardiovascular diseases as the only predictor of the discontinuation of the first anti-TNF drug¹⁸.

Focusing on the effect of DMARD co-administration, it should be considered that in the NOR-DMARD registry, the combination of MTX with an anti-TNF drug did not yield a better clinical response than anti-TNF monotherapy, and that the effect of MTX on longer drug survival was seen only for IFX¹⁷. In the DANBIO registry, the concomitant use of MTX at baseline did not affect the drug persistence, but in the multivariate regression model, the lack of MTX was correlated with anti-TNF drug discontinuation⁷. Further, in the SSATG registry concomitant MTX improved TNF drug adherence by reducing the number of dropouts for adverse events⁸. These discrepancies, apart from several confounding factors, might occur because in the retrospective analysis from registries, concomitant DMARD treatment is often related to baseline, while information about ongoing DMARD therapy is often missing or incomplete. In our study, data on DMARD and glucocorticoid dosage were collected or retrieved from patient charts over time, and we showed that DMARD combination significantly dropped from 58.4% at entry to 42.9% at 3 years, and further decreased to 37.8% at 4 years. These findings may explain

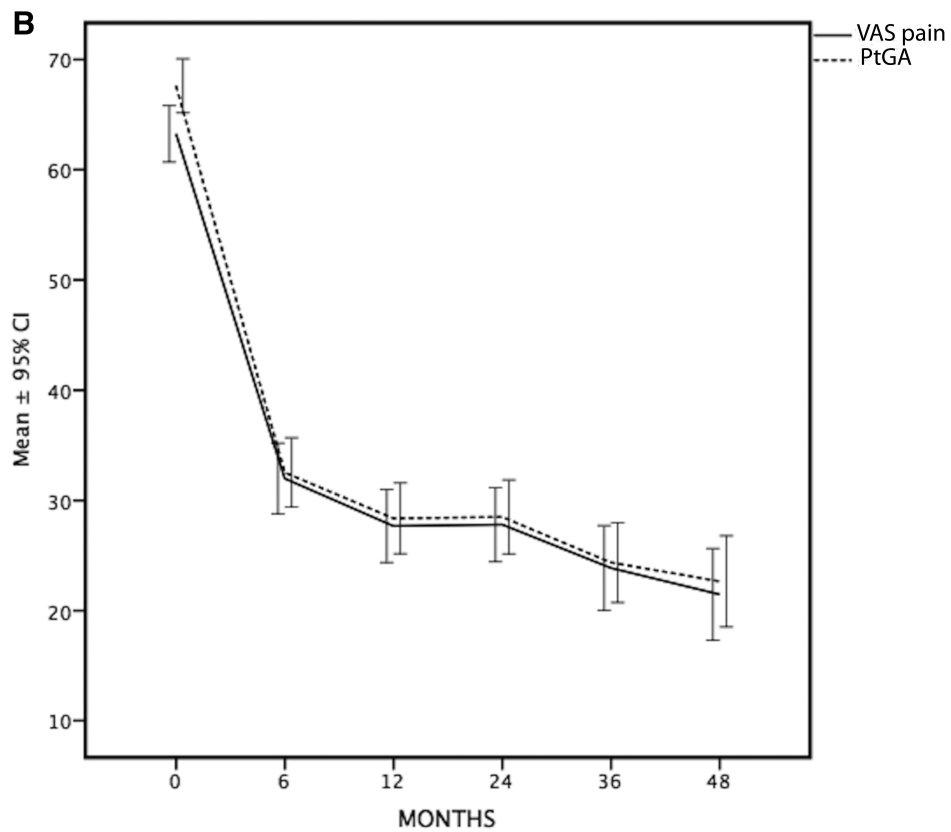
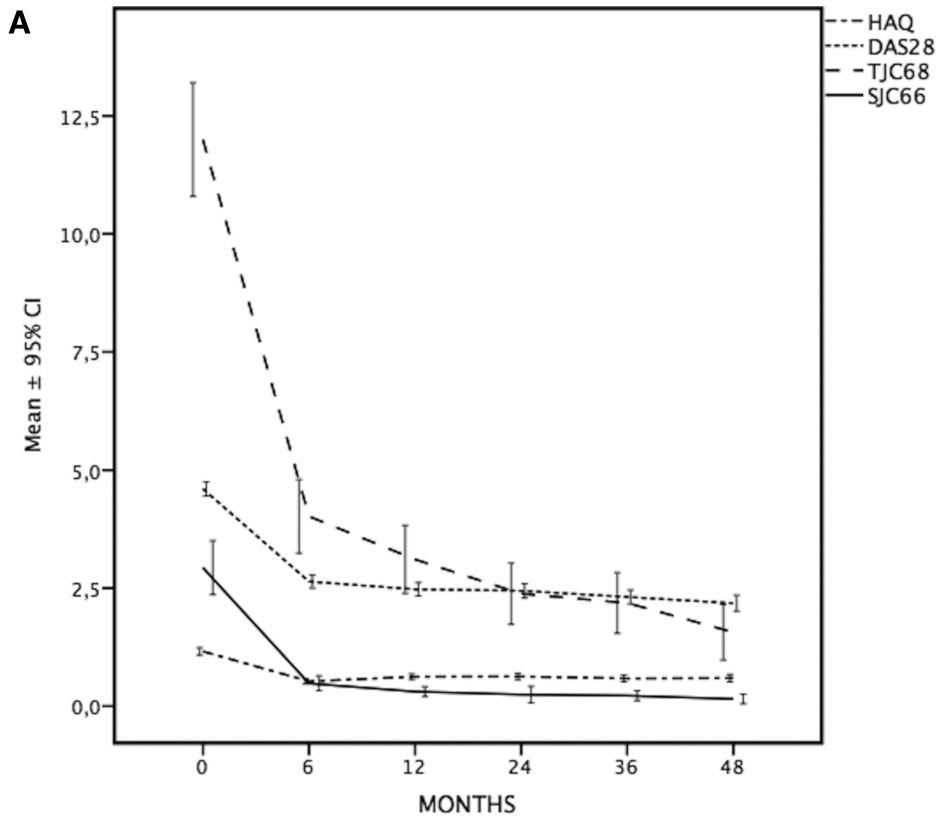


Figure 3. Four-year values (mean \pm 1 SD). A. 68 tender joint count (TJC), 66 swollen joint count (SJC), 28-joint disease Activity Scores (DAS28), Health Assessment Questionnaire (HAQ). B. Visual analog scale (VAS) of pain, patient global assessment of disease activity (PtGA). A rapid decrease is shown at 6 months that was sustained up to 48 months.

why baseline DMARD co-therapy does not correlate with clinical outcomes in all studies, and provide evidence that in settings of standard care, Italian rheumatologists tend to stop concomitant DMARD once a clinical improvement is achieved in patients with PsA taking anti-TNF therapy.

The secondary endpoint of this analysis was to assess the possible effect of TNF inhibitors on glucocorticoid intake in PsA, and we have shown that the frequency of patients taking prednisone and its mean daily dosage significantly decreased during 4 years of followup. However, a controlled trial is needed to confirm a definitive steroid-sparing effect of anti-TNF treatment. The effectiveness of anti-TNF therapy was assessed by “good” EULAR response, changes in 68-TJC and 66-SJC, and patient-reported outcomes. The percentage of patients attaining a “good” EULAR response ranged between 59% and 73% at 6 months and increased up to 64%–86% at 4 years. Patients taking IFX had the best response rates probably because they had the highest disease activity, and DAS28 decrease ≥ 1.2 from baseline was easier to achieve. At 6 months, 68-TJC and 66-SJC as well as HAQ, PtGA, and VAS pain rapidly dropped and then further decreased slightly up to 4 years.

Our study has the usual drawbacks of retrospective analysis such as the lack of randomization of unselected patients or the bias of channeling PsA patients with more active disease who were taking IFX. Thus, definite conclusions cannot be drawn about the longterm effectiveness of different anti-TNF drugs. Nevertheless, there are some strong points to be highlighted, such as the high 4-year drug survival of TNF blocking agents and the sustained good clinical outcomes in PsA. Finally, to our knowledge, this is the first study from real-world settings showing how anti-TNF treatment is associated with a meaningful lowering of glucocorticoid need across years.

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