Arthritis Care & Research
Vol. 68, No. 4, April 2016, pp 432–439
DOI 10.1002/acr.22788


ORIGINAL ARTICLE

# Twelve-Year Retention Rate of First-Line Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: Real-Life Data From a Local Registry

ENNIO GIULIO FAVALLI,[1] FRANCESCA PREGNOLATO,[2] MARTINA BIGGIOGGERO,[3] ANDREA BECCIOLINI,[1] ALESSANDRA EMILIANA PENATTI,[3] ANTONIO MARCHESONI,[1] AND PIER LUIGI MERONI[4]

***Objective.*** **To evaluate the 12-year survival of the first tumor necrosis factor inhibitor (TNFi) treatment in a cohort of rheumatoid arthritis (RA) patients, comparing the between-groups discontinuation rates for infliximab, etanercept, and adalimumab.**

***Methods.*** **RA patients treated with their first TNFi were investigated from a local registry. Before and after adjusting for propensity scores, overall and by individual TNFi 12-year drug retention was evaluated. Drug survival rates were calculated using the Kaplan-Meier method and compared by the Cox extended model. Subanalyses were performed according to concomitant methotrexate (MTX) and discontinuation reasons.**

***Results.*** **Of 583 patients, 222 were treated with infliximab, 179 with etanercept, and 182 with adalimumab; 33.7% and 26% discontinued the first TNFi because of inefficacy or adverse events, respectively. The overall 12-year drug survival rate for the unmatched population was 23.4%. In the propensity score–adjusted population, the hazard ratio (HR) for treatment discontinuation was significantly greater for adalimumab and infliximab versus etanercept (HR 2.89 [95% confidence interval (95% CI) 2.2–3.78] and HR 2.56 [95% CI 1.92–3.4], respectively), and no difference was found between and for adalimumab versus infliximab (HR 1.16 [95% CI 0.91–1.47]). The incidence of withdrawal due to secondary inefficacy was stable from 3 to 12 years for etanercept, but progressively increased for the monoclonal antibodies. Concomitant MTX significantly increased the survival of both adalimumab and etanercept (HR 1.48 [95% CI 1.18–1.86]).**

***Conclusion.*** **The overall 12-year drug survival rate was 23.4%, being significantly higher for etanercept than adalimumab and infliximab. Etanercept discontinuations for inefficacy did not increase from 3 to 12 years. Concomitant MTX increased adalimumab and etanercept drug survival.**

## INTRODUCTION

The development of biologic agents in the late 1990s has dramatically improved the management of rheumatoid arthritis (RA). Tumor necrosis factor inhibitor (TNFi) therapies were the first biotherapies to be developed in rheumatology, and over the last decade have become the most frequently prescribed class of biologic drugs for the treatment of RA patients who failed traditional synthetic disease-modifying antirheumatic drugs (sDMARDs). Currently, 5 TNFi have been licensed for RA by the European Medicines Agency and the US Food and Drug Administration, and 3 of them (infliximab, etanercept, and adalimumab) are the most widely used in clinical practice.

Despite the abundant evidence of TNFi efficacy and safety profile from randomized controlled trials (RCTs) (1–6), data on the long-term effects of TFNi remain relatively scarce. Moreover, the external validity of RCTs is dramatically hampered by stringent inclusion and exclusion

[1]Ennio Giulio Favalli, MD, Andrea Becciolini, MD, Antonio Marchesoni, MD: Gaetano Pini Institute, Milan, Italy; [2]Francesca Pregnolato, MS: Experimental Laboratory of Immunological and Rheumatologic Researches, IRCCS Istituto Auxologico Italiano, Milan, Italy; [3]Martina Biggioggero, MD, Alessandra Emiliana Penatti, MD: University of Milan and Gaetano Pini Institute, Milan, Italy; [4]Pier Luigi Meroni, MD: University of Milan and IRCCS Istituto Auxologico Italiano, Milan, Italy.

Dr. Favalli has received speaking fees (less than $10,000 each) from BMS, Roche, MSD, UCB, Pfizer, and AbbVie. Dr. Marchesoni has received speaking fees (less than $10,000 each) from BMS, Roche, MSD, UCB, Pfizer, and AbbVie. Dr. Meroni has received speaking fees (less than $10,000 each) from BMS, Roche, MSD, UCB, Pfizer, and AbbVie.

Address correspondence to Ennio Giulio Favalli, MD, Department of Rheumatology, Gaetano Pini Institute, Milan, Via Gaetano Pini, 9, 20122 Milan, Italy. E-mail: ennio.favalli@gmail.com.

Submitted for publication July 25, 2015; accepted in revised form November 3, 2015.

## Significance & Innovations

- The 12-year retention rate of a first-line tumor necrosis factor inhibitor was 23.4%.
- Compared with both monoclonal antibodies, etanercept showed a significantly better short- and long-term drug survival.
- The incidence of withdrawal due to secondary inefficacy was stable from 3 to 12 years for etanercept, but progressively increased for the monoclonal antibodies.
- The combination therapy with methotrexate increased the survival on treatment of both etanercept and adalimumab.

criteria, therefore limiting generalization to daily clinical practice (7). Because of these reasons, large population-based national registries have been increasingly used to investigate the long-term performance of TNFi in a real-life setting, despite the possible lack of the controlled characteristic of RCTs (8).

Drug survival may be considered a reliable indicator of overall treatment effectiveness in observational registries, as it is determined by drug efficacy, its safety profile, and several other factors that influence the drugs' use, such as patients' compliance, number of alternative treatment options available, and characteristics of the treated population. Therefore, many studies from European and US biologic drug registries have provided data about overall TNFi drug retention in RA, as well as comparing in a few cases the relative drug persistence of etanercept, infliximab, and adalimumab, and the different drug survival of the first and subsequent lines of TNFi therapy (9–13). Despite the extensive use of drug survival in some pharmacoepidemiologic studies of TNFi in RA, the length of the analyzed followup period has been often limited to no more than 5 years.

The aim of this study is to evaluate for the first time the long-term (12 years) drug survival in a large population-based cohort of RA patients who received a TNFi as first-line biologic treatment, comparing the between-group discontinuation rates for each TNFi (infliximab, etanercept, and adalimumab) and analyzing the role of concomitant sDMARD treatment.

## MATERIALS AND METHODS

**Study population.** Data from all RA patients treated with a biologic agent between October 1999 and December 2014 in our rheumatology unit were collected in a local registry and approved by the local ethics committee. Patients ages ≥18 years fulfilling the American College of Rheumatology 1987 revised criteria (14) were enrolled after giving their written informed consent. For all patients, the database included demographic features (age, sex, and time since RA diagnosis); clinical parameters (Disease Activity Score in 28 joints [DAS28], Simplified Disease Activity Index [SDAI], Clinical Disease Activity Index [CDAI], rheumatoid factor [RF] positivity, C-reactive protein [CRP] level and erythrocyte sedimentation rate [ESR], and Health Assessment Questionnaire [HAQ] disability index [DI] score); and therapeutic data (biologic therapy and concomitant sDMARDs and steroids use). All the mentioned disease and treatment followup data were collected at baseline and then every 6 months until December 15, 2014. This analysis was conducted including only patients who received infliximab, etanercept, or adalimumab as first-line biotherapy. In order to balance the exposure among the considered biologic drugs, the evaluation was limited to the period when all 3 TNFi were available in Italy (from January 2003) in a setting with relatively similar access to each drug. Exclusion criteria were a previous therapy with a different biologic drug or the enrollment in an RCT. Treatments were administered in routine care in accordance with RA good clinical practice; TNFi were prescribed in almost every case according to the licensed regimen, and concomitant sDMARDs or corticosteroids were administered if ordered by the referring rheumatologist. Drug survival was retrospectively calculated as the time period until the definitive treatment interruption or the first missed dose after initiation of TNFi therapy. Interruptions 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 December 15, 2014. The reasons for TNFi discontinuation were analyzed and classified into 3 major categories: inefficacy (primary and secondary no response), adverse events (AEs), and others (including remission, desire for pregnancy, and patient preference). The latter was considered as right-censored in the drug-survival analysis.

Further subanalyses were conducted by stratifying the study population according to concomitant methotrexate (MTX) treatment and median dosage (≤10 mg/week versus >10 mg/week) as predictor of discontinuation and the reason for TNFi replacement.

**Statistical analysis.** Descriptive statistics were used to calculate mean and SD, and median and interquartile range. Differences between treatment groups were analyzed by the Kruskal-Wallis nonparametric test for continuous variables and chi-square test for categorical variables. Parametric or nonparametric correlations between variables was determined by Pearson's or Spearman's coefficient, respectively. Survival distribution curves were first computed on unmatched data by the Kaplan-Meier method and compared statistically by a stratified log rank test. Moreover, propensity scores (PS)–analysis was applied for adjusting selection bias due to the retrospective study design and lack of randomization (see Supplementary Appendix A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22788/abstract) (15). PS were calculated for each patient using logistic regression with TNFi (infliximab, etanercept, or adalimumab) as the dependent variable and the following baseline characteristics as independent variables: disease duration, DAS28, HAQ score, and concomitant corticosteroid use. Since only subcutaneous TNFi may be used as monotherapy according to what is reported in product labels, concomitant MTX treatment was excluded

**Table 1. Baseline characteristics of the 3 groups of patients according to the TNF inhibitor***

| | Unmatched | | | | Matched | | | |
|---|---|---|---|---|---|---|---|---|
| | IFX (n = 222) | ADA (n = 182) | ETN (n = 179) | *P* | IFX (n = 257) | ADA (n = 251) | ETN (n = 243) | *P* |
| Demographics | | | | | | | | |
| Age, years | 54.6 (46.4–63.0) | 54.6 (43.1–64.2) | 53.3 (44.4–63.2) | 0.915 | 51.2 (44.0–61.5) | 54.3 (43.9–61.5) | 52.9 (44.3–63.2) | 0.048 |
| Female, % | 85.1 | 82.4 | 79.9 | 0.384 | 78.6 | 80.9 | 79.8 | 0.815 |
| Clinical features | | | | | | | | |
| Disease duration, years | 8.5 (4.4–15.6) | 9.3 (5.4–16.8) | 7.7 (4.3–14.9) | 0.165 | 9.9 (4.8–17.6) | 8.0 (4.7–16.0) | 8.8 (5.0–15.1) | 0.650 |
| RF, % | 82.9 | 84.6 | 83.8 | 0.895 | 79.4 | 84.1 | 83.1 | 0.344 |
| ESR, mm/hour | 40 (27–63) | 35 (22–54) | 40 (25–58) | 0.020 | 35 (23–60) | 35 (24–54) | 35 (23–56) | 0.355 |
| CRP, mg/liter | 2.2 (0.9–4.2) | 1.3 (0.5–2.6) | 1.5 (0.8–3.0) | < 0.001 | 1.7 (0.6–3.5) | 1.3 (0.5–2.8) | 1.4 (0.7–2.4) | 0.195 |
| DAS28 (ESR) | 5.8 (5.1–6.6) | 5.2 (4.3–5.9) | 5.4 (4.6–6.1) | < 0.001 | 5.3 (4.3–6.1) | 5.2 (4.3–6.0) | 5.2 (4.5–6.0) | 0.328 |
| SDAI | 32.3 (23.0–41.8) | 24.8 (17.8–33.6) | 24.7 (18.3–34.4) | < 0.001 | 26.0 (18.1–33.6) | 24.8 (17.5–33.7) | 24.2 (18.1–34.3) | 0.757 |
| CDAI | 29.0 (21.0–37.9) | 22.6 (15.6–30.7) | 23.4 (16.3–31.0) | < 0.001 | 22.5 (16.0–31.0) | 22.5 (15.6–30.7) | 22.5 (16.5–30.4) | 0.765 |
| HAQ DI | 1.87 (1.50–2.13) | 1.25 (1.00–1.63) | 1.50 (1.00–1.88) | < 0.001 | 1.38 (1.00–1.88) | 1.37 (1.00–1.67) | 1.25 (1.00–1.75) | 0.613 |
| Corticosteroids, % | 86.0 | 74.7 | 78.2 | 0.014 | 78.6 | 75.7 | 76.5 | 0.727 |
| MTX, % | 94.1 | 72.5 | 72.1 | < 0.001 | 91.1 | 75.7 | 72.8 | < 0.001 |
| MTX dose, median (IQR), mg/week | 10 (10–12.5) | 10 (10–15) | 12.5 (10–15) | 0.003 | 10 (10–12.5) | 10 (10–15) | 12.5 (10–15) | 0.002 |

* Values are the mean (95% confidence interval) unless otherwise indicated. Kruskal-Wallis nonparametric test was used for continuous variables and chi-square test for categorical variables. TNF = tumor necrosis factor; IFX = infliximab; ADA = adalimumab; ETN = etanercept; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein level; DAS28 = Disease Activity Score in 28 joints; SDAI = Simple Disease Activity Index; CDAI = Clinical Disease Activity Index; HAQ = Health Assessment Questionnaire; DI = disability index; MTX = methotrexate; IQR = interquartile range.

from the statistical model. PS were then used for matching triplets based on the smallest standardized difference. The caliper is specified in standard units, so 0.25 corresponds to one-quarter of 1 SD. Survival analysis accounting for competing risks was used to provide predictions of inefficacy (primary and secondary nonresponse) and AEs. A Cox extended model was run to estimate hazard ratios (HRs) for discontinuation, since the Shoenfeld residual test showed that proportional hazard assumption was violated. Confidence intervals (CIs) at 95% for HRs were calculated.

Statistical analyses were performed using R for Windows (16). *P* values equal to or less than 0.05 were considered statistically significant.

## RESULTS

**Baseline characteristics.** The study population was selected from all RA patients (n = 756) treated with a first-line biotherapy in our rheumatology department between 2003 and 2014. According to described selection criteria, 173 patients were excluded from the analysis (141 treated with a biologic agent other than infliximab, etanercept, or adalimumab, and 32 because of missing data). The baseline demographic and clinical characteristics of the 583 enrolled patients (222 infliximab, 179 etanercept, 182 adalimumab) are reported in Table 1. Overall, 82.8% were women, the mean age was 54.2 years, the median disease duration was 8.6 years, the mean DAS28 score was 5.53, and the mean HAQ DI score was 1.5. As expected, the proportion of patients who received concomitant MTX treatment was significantly higher in the infliximab patients (94.1%) than in the etanercept (72.1%) and adalimumab (72.5%) patients. The median MTX dosage was significantly higher ($P = 0.003$) in the etanercept group (12.5 mg/week) compared with both infliximab (10 mg/week) and adalimumab (10 mg/week). No statistically significant differences existed among the 3 subgroups of treatment for age ($P = 0.91$), sex ($P = 0.38$), disease duration ($P = 0.16$), and RF positivity ($P = 0.89$). However, mean values of ESR ($P = 0.02$), CRP level ($P < 0.0001$), DAS28 ($P < 0.0001$), SDAI ($P < 0.0001$), CDAI ($P < 0.0001$), and HAQ DI ($P < 0.0001$) scores were significantly different in the 3 groups, with all being higher in infliximab-treated patients than in etanercept- and adalimumab-treated patients. After adjustment for PS, we obtained 3 homogeneous groups matched according to all the considered baseline variables (Table 1).

**Drug survival analyses.** The overall 12-year retention rate was 23.4% (95% CI 18.2–30.1) with a median survival of 53.5 months (27.8 for adalimumab, 44.2 for infliximab, and >53.5 for etanercept) (Figure 1). The HR for treatment discontinuation was significantly greater for adalimumab and infliximab versus etanercept; no difference was found

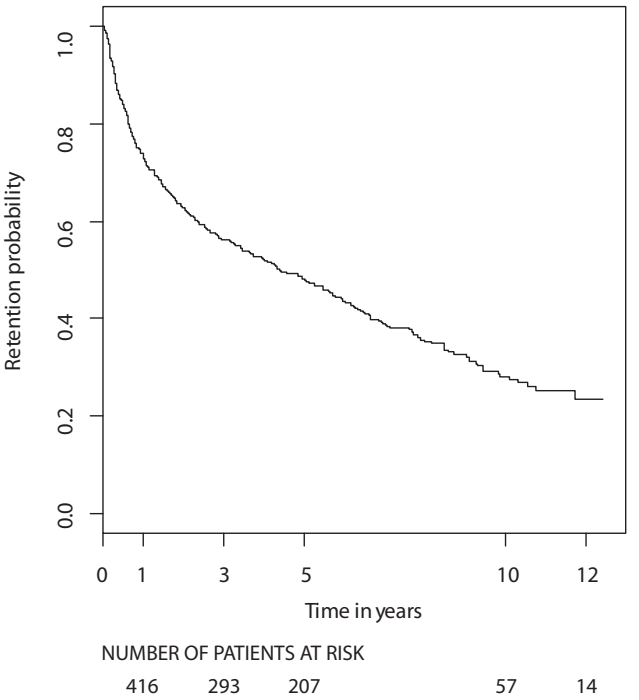


**Figure 1.** Twelve-year overall drug survival on first tumor necrosis factor inhibitor.

between infliximab and adalimumab. The estimated proportions of patients maintaining etanercept, adalimumab, and infliximab treatment were, respectively, 70.2%, 43.2%, and 55.4% after 3 years; 65.4%, 36.5%, and 44.3% after 5 years; and 52.5%, 20.3%, and 17.2% after 12 years (Figure 2).

In the PS-adjusted population, the estimated proportions of patients maintaining etanercept, adalimumab, and infliximab treatment were, respectively, 72.2%, 41.3%, and 55.6% after 3 years; 69.7%, 34.7%, and 47.3% after 5 years; and 60.2%, 18.4%, and 19.2% after 12 years (Figure 2). The HR for treatment discontinuation was significantly greater for adalimumab and infliximab versus etanercept (2.89 [95% CI 2.2–3.78] and 2.56 [95% CI 1.92–3.4], respectively); no difference was found between adalimumab versus infliximab (HR 1.16 [95% CI 0.91–1.47]). The observational period was stratified into 4 subperiods according to treatment duration. During the first 6 months, lower HRs were observed for infliximab versus etanercept and adalimumab, and for etanercept versus adalimumab. Significantly lower HRs were observed for etanercept versus adalimumab and infliximab patients over 6 months of treatment (between 6 months and 3 years, between 3 and 5 years, and over 5 years). Significantly lower HRs were observed for infliximab versus adalimumab between 6 months and 3 years. No statistically significant differences in the HRs were seen between infliximab and adalimumab at each time over 3 years of treatment (Table 2).

The comparative survival analysis of TNFi monotherapy versus association with MTX was limited to subcutaneous TNFi, since 94.1% of infliximab initiators received the biologic drug in combination (Table 1). The drug retention was significantly higher for MTX concomitant users compared with TNFi monotherapy (HR 1.48, 95% CI 1.18–1.86) (Figure 3A). The median survival for both etanercept monotherapy and combination therapy was >53.5 months, whereas for adalimumab it was 15.4 and 34.2 months, respectively. After stratification according to MTX median dosage (<15 or ≥15 mg/week), the retention rate was significantly better in high-dose subgroups compared with low-dose MTX subgroups only in

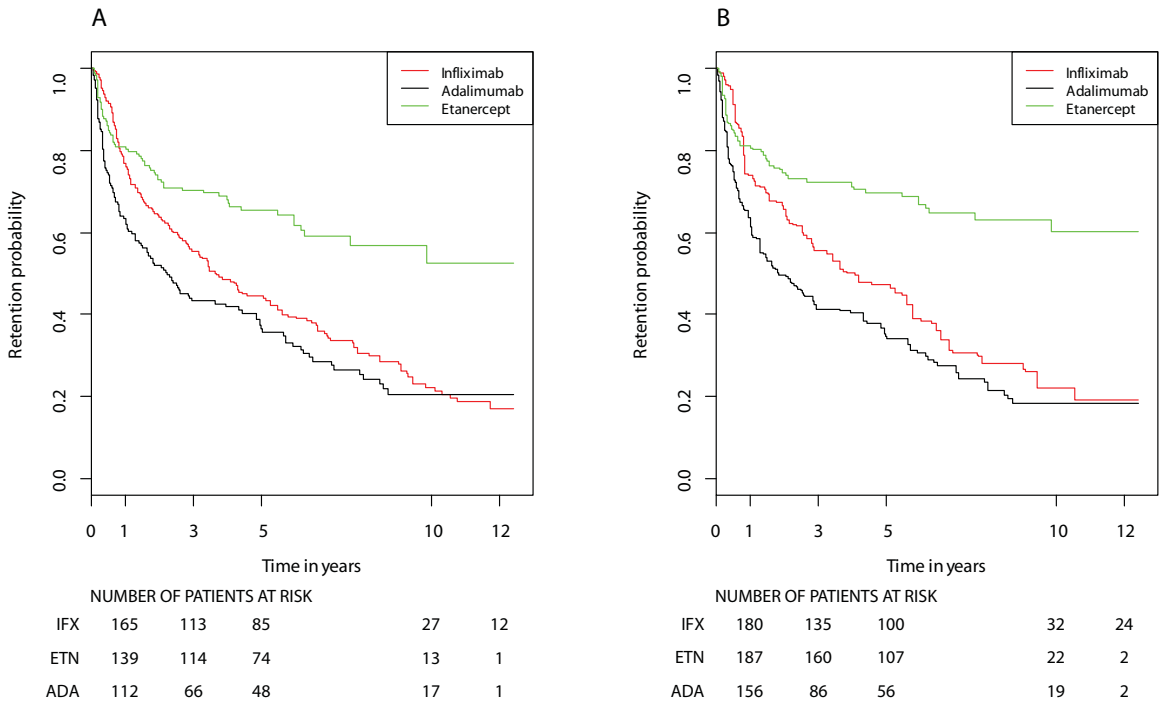


**Figure 2.** Twelve-year drug survival rates, by tumor necrosis factor inhibitor, in the unmatched (**A**) and matched (**B**) cohorts. IFX = infliximab; ETN = etanercept; ADA = adalimumab.

**Table 2. HRs for discontinuation among TNF inhibitors by treatment period***

| Treatment period/drug comparison | HR (95% CI)† | *P* |
|---|---|---|
| <6 months | | |
| Adalimumab vs. etanercept | 1.46 (1.04–2.06) | 0.03 |
| Infliximab vs. etanercept | 0.54 (0.33–0.89) | 0.016 |
| Adalimumab vs. infliximab | 1.11 (1.04–1.19) | 0.003 |
| ≥6 months to <3 years | | |
| Adalimumab vs. etanercept | 3.06 (2.09–4.48) | < 0.0001 |
| Infliximab vs. etanercept | 2.6 (1.79–3.79) | < 0.0001 |
| Adalimumab vs. infliximab | 1.16 (1.01–1.33) | 0.04 |
| ≥3 to <5 years | | |
| Adalimumab vs. etanercept | 12.82 (1.95–84.19) | 0.008 |
| Infliximab vs. etanercept | 16.66 (2.32–119.66) | 0.005 |
| Adalimumab vs. infliximab | 1.14 (0.91–1.43) | 0.26 |
| ≥5 years | | |
| Adalimumab vs. etanercept | 5.38 (1.32–21.94) | 0.019 |
| Infliximab vs. etanercept | 3.57 (1.08−11.73) | 0.036 |
| Adalimumab vs. infliximab | 1.24 (0.65–2.36) | 0.517 |

* TNF = tumor necrosis factor; HR = hazard ratio; 95% CI = 95% confidence interval.
† Cox extended model.

infliximab (HR 0.59, 95% CI 0.35–0.98) and adalimumab (HR 0.54, 95% CI 0.29–0.99), but not in etanercept users (HR 0.60, 95% CI 0.27–1.32). Moreover, no significant difference was found in drug survival of etanercept plus low-dose MTX subgroup compared with both infliximab (HR 0.95, 95% CI 0.34–2.68) and adalimumab (HR 0.92, 95% CI 0.39–2.22) plus high-dose MTX subgroups (Figure 3B).

**Reasons for discontinuation.** Overall, 197 patients (33.7%) stopped the first course of TNFi because of inefficacy (45 [7.7%] due to primary no response) and 152 (26%) because of AEs. Etanercept showed a lower frequency of discontinuation because of both inefficacy (17.5%, 44.1%, and 50.4% for etanercept, infliximab, and adalimumab, respectively; $P < 0.0001$) and AEs (22.4%, 36.7%, and 31.2% for etanercept, infliximab, and adalimumab, respectively; $P < 0.0001$). No significant differences in the comparison of the reasons for discontinuation were observed between the 2 monoclonal antibodies.

Figure 4 shows the cumulative incidence for retention failure due to inefficacy or AEs over time. The incidence of discontinuation similarly increased over time for all 3 TNFi after the first 3 years of treatment, being lower at each time for etanercept compared with the monoclonal antibodies. It is noteworthy that the incidence of drug withdrawal because of secondary inefficacy progressively increased

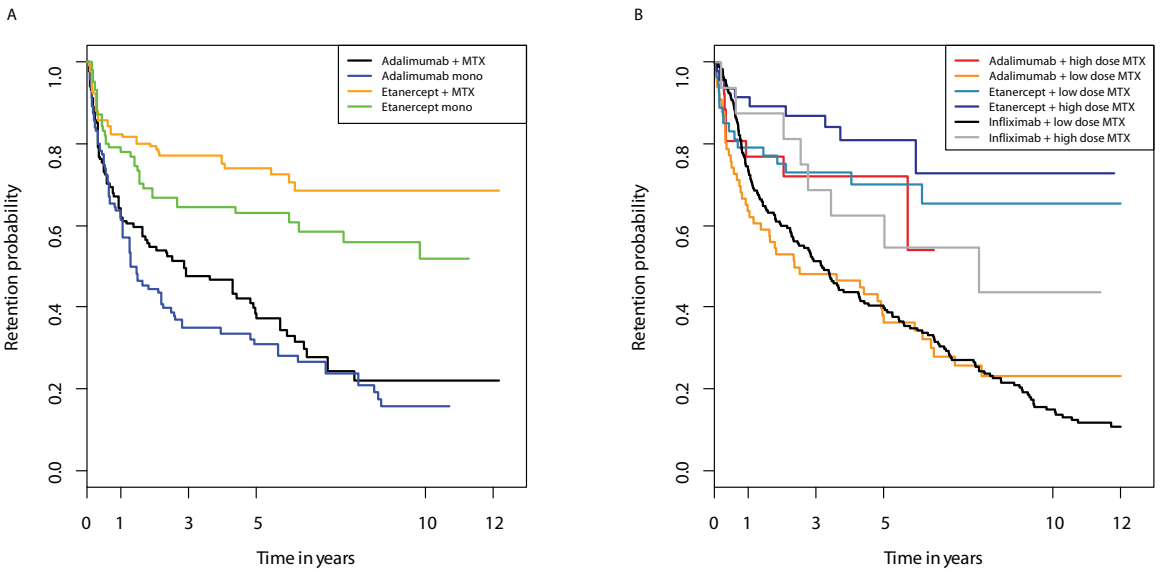


**Figure 3.** Twelve-year drug survival rates according to (**A**) concomitant methotrexate (MTX) treatment and (**B**) MTX dosage (low dosage: <15 mg/week and high dosage: ≥15 mg/week).

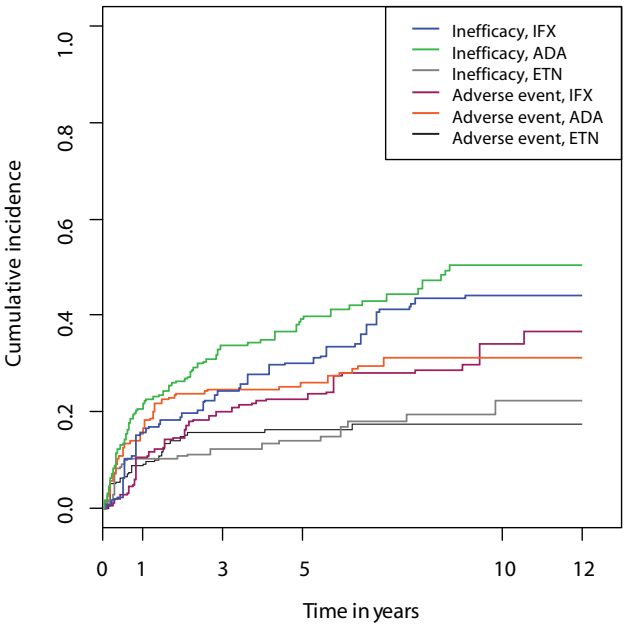


**Figure 4.** Cumulative incidence of discontinuation for inefficacy and adverse events by tumor necrosis factor inhibitor. IFX = infliximab; ADA = adalimumab; ETN = etanercept. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/acr.22788/abstract.

only for adalimumab and infliximab, but it was substantially stable for etanercept from 3 to 12 years of therapy.

## DISCUSSION

In this study we investigated the long-term retention rates for first-line TNFi in a large sample of routine-care RA patients, comparing adalimumab, etanercept, and infliximab. The study was carried out from 2003 to 2014, when all 3 drugs were available in Italy. Our data demonstrated that the overall estimated percentage of patients continuing the first biologic treatment after 12 years was 23.4% (median time-on-drug 53.5 months), with a statistically significant difference in favor of etanercept compared with both anti-TNF monoclonal antibodies. The most frequent reason for discontinuation was inefficacy (33.7%), as compared with AEs (26%). Concomitant MTX treatment significantly increased the retention rate of both adalimumab and etanercept.

This is the first report evaluating the 12-year discontinuation rate of TNFi in daily clinical practice, whereas the vast majority of previous studies analyzed a shorter followup period often limited to no more than 5 years. The short-term survival rates in our sample are comparable to those previously described in international registries, such as the British Society for Rheumatology Biologics Register (42% at 5 years) (17), the Anti-Rheumatic Therapy in Sweden registry (approximately 50% at 5 years) (10), the Gruppo Italiano di Studio sulla Early Arthritis (GISEA) registry (42% at 4 years) (11), and the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry (55% and 45% at 3 and 5 years, respectively) (18). Compared with our 12-year data, these findings suggest that the overall discontinuation rate of the first TNFi is higher during the first 3–5 years of treatment and becomes progressively lower in patients maintaining the biologic drug over 5 years. After adjusting for baseline confounding factors, we showed the overall higher drug survival of etanercept compared with both monoclonal antibodies, similarly to what is reported by the Lombardy Rheumatology Network (LORHEN) (9) and GISEA (11) registries and by a multicentric study carried out in France (19). At variance, some European studies did not find any significant difference between the 2 subcutaneous TNFi (18,20–24), whereas US reports showed greater drug survival on infliximab compared with both adalimumab and etanercept (12,20). These apparently discrepant findings might be due to differences in the baseline characteristics of the cohorts, in the regimen of administered treatments, or other methodologic variations.

Consistent with what was reported by the previously mentioned studies, this favorable etanercept result was already evident at the 3-year evaluation, but in our analysis became progressively greater from the fourth year of treatment. After stratification according to treatment duration, we found that the relationship among the 3 TNFi retention rates varied over time. In the first 6 months of therapy, the HR for discontinuing adalimumab was significantly higher compared with both etanercept and infliximab, and etanercept showed a higher HR compared to infliximab. During the subsequent entire followup period, etanercept survival on treatment was significantly greater than both adalimumab and infliximab, and became the highest, especially between 3 and 5 years of treatment. No significant differences were found between the 2 monoclonal antibodies after 3 years of treatment. Despite a shorter followup period, a similar trend was reported by Neovius et al (10), who showed adalimumab to have a greater HR for discontinuation versus etanercept only during the first year, and no difference versus infliximab during the first year.

In our cohort, etanercept showed both a better clinical efficacy and a more favorable safety profile compared with monoclonal antibodies in the first 3 years of therapy, resulting in a greater survival on treatment. Similar data were observed by the Danish Registry for Biologic Therapies in Rheumatology (21), whereas the results from other national registries such as DREAM (18), Swiss Clinical Quality Management (23), LORHEN (9), and Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study (25) are controversial. Moreover, we showed that the difference in drug survival between etanercept and the monoclonal antibodies became progressively greater over time. Although etanercept was significantly better tolerated than monoclonal antibodies across the entire followup period, resulting in a lower frequency of withdrawal due to AEs, the crucial factor is the lower number of long-term secondary no response due to etanercept inefficacy. This trend is particularly evident especially after 3 years of treatment, when the cumulative incidence of discontinuation due to inefficacy remained stable over time in etanercept-treated patients (from 15.7% at 3 years to 17.5% at 12 years), but progressively increased in both infliximab-treated (from 24.4% at 3 years to 44.1% at 12 years) and adalimumab-treated (from 33.9% at 3 years to 50.4% at 12 years) groups. The development of infliximab and adalimumab antidrug

antibodies should be considered as a potential factor leading to secondary loss of clinical response, since it has been suggested that the incidence of etanercept antidrug antibodies is significantly lower and clinically less important (26,27). It has been also reported that the proportion of patients developing antidrug antibodies increases at least over 3 years (26), possibly explaining the effect on monoclonal antibodies' long-term efficacy observed in our cohort. Moreover, cotreatment with sDMARDs was also an independent predictor for drug retention in the Hellenic Registry of Biologics (24) and the GISEA registry (11). sDMARDs (mainly MTX) may be effective as nonbiologic antirheumatic drugs themselves, but they may also potentiate the anti-TNF therapy by effectively inhibiting the formation of antidrug antibodies (28,29). In fact, the results of our subanalysis according to concomitant MTX use confirmed that the 12-year retention rate is significantly greater in MTX recipients compared with both etanercept or adalimumab monotherapy. Moreover, a relationship between drug survival and an MTX weekly dose was found only in adalimumab and infliximab treatment groups, confirming the crucial role of combination therapy, especially in patients receiving anti-TNF monoclonal antibodies. In any case, the overall better drug retention of etanercept compared with infliximab and adalimumab may be only partially explained by the higher baseline median MTX dose.

The main limitation of the current study is related to its observational and retrospective design. In the absence of randomization, patients with a different discontinuation risk may have been channeled to a specific drug, producing selection bias and potentially affecting our analysis. However, we tried to minimize the observed differences in baseline characteristics among the 3 treatment groups by the application of PS matching, obtaining 3 homogeneous populations before the retention rate analysis. Moreover, our results were similar in the unmatched and matched populations. Since only subcutaneous TNFi may be used as monotherapy, according to what is reported in product labels, concomitant MTX treatment was excluded from the statistical model. Considering the significantly higher proportion of patients receiving concomitant MTX in the infliximab group as recommended in the product label, the combination with MTX has not been included as a variable in the PS statistical model, but survival subanalyses according to the MTX median dose were subsequently performed in the matched population. The results of those additional evaluations may be partially affected by the small subgroup sample size. We also limited our analysis to the period when all 3 TNFi were available in Italy in order to avoid any influence on treatment survival analysis. Residual confounding factors can still remain due to unknown and unmeasured channeling variables associated with the outcome. On the other hand, the most important strength is the very long followup period, which allowed for the first time the evaluation of a 12-year retention rate and the stratification of the treatment duration in 3-year subperiods in order to better analyze the differences in short- and long-term drug survival, as well as the time distribution of reasons for drug discontinuation.

In conclusion, we have presented the first observational data on 12-year retention rate of the first-line TNFi, comparing 3 anti-TNF agents after adjusting for potential confounding factors. Compared with both monoclonal antibodies, etanercept showed a better short- and long-term drug survival because of a most favorable safety profile and especially a lower incidence of long-term secondary no responses. The combination therapy with MTX increased the survival on treatment of both etanercept and adalimumab, with a significant dose relationship only for monoclonal antibodies. Our findings may suggest the preferential use of etanercept as first-line TNFi, mainly in patients intolerant to MTX. Future additional analyses in a larger population should be advocated in order to confirm our results.

## ACKNOWLEDGMENT

The authors are grateful to Dr. Jessica Chiesa for revising the manuscript.

### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Favalli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Favalli, Meroni.
**Acquisition of data.** Biggioggero, Becciolini, Penatti, Marchesoni.
**Analysis and interpretation of data.** Favalli, Pregnolato, Biggioggero, Becciolini.

## REFERENCES

1. Lipsky PE, van der Heijde DM, St.Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000;343:1594–602.
2. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675–81.
3. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti–tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–11.
4. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2005;54:26–37.
5. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375–82.
6. St.Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004;50:3432–43.
7. Wolfe F. Why results of clinical trials and observational studies of anti-tumour necrosis factor (anti-TNF) therapy differ:

methodological and interpretive issues. Ann Rheum Dis 2004;63 Suppl 2:ii13–7.
8. Caporali R, Pallavicini FB, Filippini M, Gorla R, Marchesoni A, Favalli EG, et al. Treatment of rheumatoid arthritis with anti-TNF-$\alpha$ agents: a reappraisal. Autoimmun Rev 2009;8: 274–80.
9. Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, et al. TNF-$\alpha$ antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 2009;1173: 837–46.
10. Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015;74: 354–60.
11. Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Long-term retention of tumor necrosis factor-$\alpha$ inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. J Rheumatol 2012;39:1179–84.
12. Greenberg JD, Reed G, Decktor D, Harrold L, Furst D, Gibofsky A, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis 2012;71:1134–42.
13. Kobayakawa T, Kojima T, Takahashi N, Hayashi M, Yabe Y, Kaneko A, et al. Drug retention rates of second biologic agents after switching from tumor necrosis factor inhibitors for rheumatoid arthritis in Japanese patients on low-dose methotrexate or without methotrexate. Mod Rheumatol 2015;25:251–6.
14. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
15. Austin PC, Platt RW. Survivor treatment bias, treatment selection bias, and propensity scores in observational research. J Clin Epidemiol 2010;63:136–8.
16. R Core Team. R: a language and environment for statistical computing. Vienna (Austria): R Foundation for Statistical Computing; 2012.
17. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL, for the British Society for Rheumatology Biologics Register. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70: 583–9.
18. Kievit W, Fransen J, Adang EM, den Broeder AA, Bernelot Moens HJ, Visser H, et al. Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. Rheumatology (Oxford) 2011;50:196–203.
19. Frazier-Mironer A, Dougados M, Mariette X, Cantagrel A, Deschamps V, Flipo RM, et al. Retention rates of adalimumab, etanercept and infliximab as first and second-line biotherapy in patients with rheumatoid arthritis in daily practice. Joint Bone Spine 2014;81:352–9.
20. Yazici Y, Krasnokutsky S, Barnes JP, Hines PL, Wang J, Rosenblatt L. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. J Rheumatol 2009;36:907–13.
21. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010;62:22–32.
22. Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, et al. TNF$\alpha$ antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 2007;74: 148–54.
23. Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A, for the Swiss Clinical Quality Management Physicians. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009;61:560–8.
24. Flouri I, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, et al. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: low rates of remission and 5-year drug survival. Semin Arthritis Rheum 2013;43:447–57.
25. Markenson JA, Gibofsky A, Palmer WR, Keystone EC, Schiff MH, Feng J, et al. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. J Rheumatol 2011;38: 1273–81.
26. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. Ann Rheum Dis 2010;69: 817–21.
27. Krieckaert CL, Jamnitski A, Nurmohamed MT, Kostense PJ, Boers M, Wolbink G. Comparison of long-term clinical outcome with etanercept treatment and adalimumab treatment of rheumatoid arthritis with respect to immunogenicity. Arthritis Rheum 2012;64:3850–5.
28. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis 2013;72:165–78.
29. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis: results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8:R174.