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Effect of Comedication With Conventional Synthetic Disease-Modifying Antirheumatic Drugs on Retention of Tumor Necrosis Factor Inhibitors in Patients With Spondyloarthritis

A Prospective Cohort Study

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Objective. **To evaluate whether use of comedication with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) influences the retention of tumor necrosis factor inhibitors (TNFi) in patients with spondyloarthritis (SpA).**

Methods. **Patients with SpA from the Rheumatic Diseases Portuguese Register who started treatment with their first TNFi between 2001 and 2014 were included in this study. Cox regression analysis was used to estimate the effect of comedication with csDMARDs on TNFi retention in 2 types of models: a model in which baseline (time-fixed) variables were included, and a second model incorporating time-varying variables, including sociodemographic features, measures of disease activity, measures of physical function, and cotreatment with other drugs (nonsteroidal antiinflammatory drugs and oral steroids). To control for possible confounding by indication, the effect of csDMARD comedication on TNFi retention was also tested after adjustment for the treatment propensity score.**

Results. **In total, 954 patients were included in the study, of whom 289 (30.3%) discontinued treatment with their first TNFi after a median follow-up time of 2.5 years (range 0.08–13 years). Inefficacy was the most common reason for TNFi discontinuation (55.7% of patients). In the multivariable analyses, comedication with csDMARDs had no measurable effect on TNFi retention, neither in the baseline model (hazard ratio [HR] 0.83, 95% confidence interval [95% CI] 0.59–1.16) nor during follow-up in the model adjusted for time-varying covariates (HR 1.07, 95% CI 0.68–1.68). The**

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effect of csDMARD comedication remained nonsignificant after propensity score adjustment.

Conclusion. **Comedication with csDMARDs does not prolong TNFi retention in patients with SpA in clinical practice, suggesting that there is no benefit conferred by the concomitant use of these drugs.**

In the last decade, treatment of patients with spondyloarthritis (SpA) with tumor necrosis factor inhibitors (TNFi) has been found to have good efficacy in several randomized controlled trials (RCTs) (1). However, in 20–40% of patients with SpA, the disease either fails to respond to treatment or responds inadequately (2). Since TNFi are expensive and not without risks, identifying a therapy (comedication) as well as patient- and disease-related features associated with improved outcomes is highly relevant. Data from RCTs have been used for this purpose (3–5), but the results from clinical trials are difficult to translate into daily practice. In addition, the limited duration of clinical trials precludes conclusions on long-term outcomes, and observational cohorts comprising "real world" patients followed up for longer periods of time may yield more valuable information that is helpful to clinicians.

The length of time during which a patient remains on therapy (referred to as TNFi retention) has been commonly used as a proxy for effectiveness in observational research (6,7). Studies of the effects of comedication with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) on TNFi retention have been reportedly inconclusive. Some studies have not shown any added benefit (8–10), whereas another recent study showed that TNFi retention was improved by csDMARD comedication (11). Obviously, results from observational studies may easily lead to spurious conclusions (12). Among other limitations, observational studies are sensitive to confounding by indication (13). Adjustment for the treatment propensity score is one of the methods to handle this form of selection bias (14), but this type of confounding was not addressed appropriately in the above-mentioned studies.

In addition, other potential predictors of TNFi discontinuation include patient- and disease-related features. However, data on these predictors in patients with SpA are still scarce, and previous studies have evaluated baseline features only (8,10,15–18). Some of these features, such as disease activity, may fluctuate over time, which is likely attributable to the effects of TNFi treatment, so that their prognostic value, fixed at baseline, may change accordingly with elapsed time. This is particularly relevant in settings where patients may continue treatment with the same drug for several years, a frequent practice in patients with SpA (9,19,20).

In this study, we addressed whether comedication with csDMARDs increases TNFi retention in patients with SpA being treated with their first TNFi. In addition, we investigated which patient- and disease-related factors would determine the discontinuation of TNFi in clinical practice. Factors that inherently fluctuate over time (time-varying covariates) were considered in the analysis in order to obtain the best estimates for prediction.

PATIENTS AND METHODS

Study design and data source. This was a multicenter, prospective, open-cohort study using data from the Rheumatic Diseases Portuguese Register (known as Reuma.pt). Reuma.pt is a nationwide clinical register that was established and is managed by the Portuguese Society of Rheumatology, in which data from patients with various rheumatic diseases are recorded by their treating rheumatologists, using standardized protocols in daily practice. A detailed report describing the design of Reuma.pt and its data management procedures has been published elsewhere (21). Reuma.pt was approved by the National Data Protection Board and by the local Ethics Committees. Patients provided their informed consent prior to inclusion in the study.

In this cohort, we included biologics-naive adult patients (ages ≥18 years) diagnosed as having SpA (excluding psoriatic arthritis) by their treating rheumatologist. All patients received their first TNFi (adalimumab, etanercept, golimumab, or infliximab) between 2001 and 2014. The baseline study visit corresponds to the start date of the first TNFi. Patients were then reassessed after 3 months of therapy, after 6 months of therapy, and thereafter every 6 months, with clinical data being recorded for each patient by the treating rheumatologist. For the current study, a dedicated team of researchers from each participating center was assigned to compare information on a core set of sociodemographic and clinical variables between the central database and the medical records, in order to complete missing information whenever possible. This data quality assessment strategy has been proven to decrease the risk of information bias (22).

Outcome and definition of exposure period. The main outcome of this study was time to first TNFi discontinuation. The exposure period (drug survival) comprised the time between the first TNFi administration and therapy discontinuation (or censoring), as well as the time period representing twice the half-life of the drug (3 days for etanercept, 9 days for infliximab, 14 days for adalimumab, and 14 days for golimumab). Cases in which patients suspended therapy but resumed the same TNFi (regardless of the time interval) were not considered discontinuations; however, this time was discounted from the exposure period. This was done in order to disregard temporary treatment pauses due to clinical reasons (e.g., infections, surgery, or pregnancy).

In order to capture adverse events occurring early in the treatment course, no minimum follow-up time was required for inclusion. Patients who did not discontinue

therapy were censored at the date of the last available visit or at the date of database extraction (February 5, 2015).

The date of discontinuation and reason for discontinuation of a TNFi (inefficacy, adverse event, or other) were recorded by the rheumatologist. Primary and secondary treatment failures were defined a posteriori (assessed after 3 months of therapy) according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) showing clinically important improvement (defined as a decrease from baseline of $\geq$1.1) (23). A patient was classified in the primary failure group if a treatment response at 3 months was not achieved, and in the secondary failure group if a treatment response at 3 months was achieved but any time was lost during the follow-up.

Clinical assessments. Clinical data included the following variables: 1) baseline sociodemographic features, including age, disease duration, sex, years of formal education, and smoking status; 2) disease activity as assessed by the ASDAS using the C-reactive protein (CRP) level, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (24), the patient's global assessment of disease activity using a 0–100-mm visual analog scale (VAS), and the patient's assessment of pain using a 0–100-mm VAS; 3) functional status as assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) (25); 4) number of painful joints (range 0–73) and number of swollen joints (range 0–75) at physical examination; 5) laboratory assessments, including measurement of the CRP level (in mg/dl) and erythrocyte sedimentation rate (in mm/hour); and 6) current medications, including the specific TNFi, comedication with csDMARDs, oral steroids, and nonsteroidal antiinflammatory drugs (NSAIDs). Except for the sociodemographic features, variables were collected at all visits.

Patients were divided into 5 categories according to the pattern of csDMARD use, as follows: 1) patients starting csDMARDs and the TNFi simultaneously; 2) patients stopping csDMARDs when starting the TNFi; 3) patients starting csDMARDs after the start of the TNFi; 4) patients continuing csDMARDs when the TNFi was started; and 5) patients who never received csDMARDs (neither before nor after starting the TNFi).

Statistical analysis. TNFi retention was assessed using Kaplan-Meier survival analysis. With this method, we estimated the annual rate of TNFi discontinuation. Using the log rank test, Kaplan-Meier estimates were compared between patients discontinuing the TNFi due to inefficacy and those discontinuing due to adverse events, and between those receiving and those not receiving csDMARD comedication. Time to discontinuation was also assessed separately for patients starting the TNFi before 2007 and those starting after 2007. This year was chosen to assess the effect of the availability of more than 2 types of TNFi on drug discontinuation (26).

Multivariable Cox proportional hazard regression was used to ascertain the association between csDMARD comedication and TNFi retention at baseline and as a time-varying covariate in separate models. Patient- and disease-related covariates were included in the multivariable models if they were considered potentially meaningful in the univariable analysis (at a significance level of $P < 0.20$) or if they were considered clinically relevant. Clinically relevant covariates were selected a priori, and these included age, sex, year of TNFi start (before or after 2007), other concomitant medications (oral steroids [yes versus no] and NSAIDs [yes versus no]), pattern of csDMARD use (n = 5), and specific TNFi (n = 4). A variable was kept in the final model if it was deemed statistically significant (at $P < 0.05$) or if it was a confounder of the association of interest (change in beta coefficient >25%). If 2 variables, which were considered to be collinear under clinical reasoning, were found to be significant separately, 2 final models were built. The Efron method was used to handle tied discontinuations (27).

Sensitivity analysis. To control for possible confounding by indication, the effect of csDMARDs on TNFi discontinuation was also assessed after propensity score adjustment. In this study, the propensity score was defined as the conditional probability of being assigned cotreatment with csDMARDs (in addition to the TNFi) given a set of observed baseline variables. This method is used in observational studies to balance covariates between 2 treatment groups (14). Age, the BASFI, the ASDAS, the number of swollen joints, sex, and year of TNFi start were selected, based on content knowledge, to estimate the propensity score, using multivariable probit regression with csDMARD treatment as the dependent variable (also using cotreatment with methotrexate or sulfasalazine as the dependent variable in separate models) (for details on the propensity score estimation, see Supplementary Methods, Supplementary Tables 1–9, and Supplementary Figures 1–6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39772/abstract). Finally, through Cox regression, we obtained a propensity score–adjusted estimate of the effect of csDMARD comedication on TNFi discontinuation. All data analyses were performed using Stata software version 12.1 (StataCorp).

RESULTS

Baseline characteristics of the patients. In total, 954 patients diagnosed as having SpA by their treating rheumatologist from 44 centers were included. Table 1 shows the baseline characteristics of the patients who discontinued their TNFi and those who remained on treatment with their TNFi, as well as patients who received csDMARD comedication and those who did not receive csDMARDs. A large proportion of patients were treated with csDMARDs at baseline (389 [41%] of 954). Patients with peripheral arthritis were more likely to receive csDMARDs than were patients without peripheral arthritis (137 [68.2%] of 201 versus 144 [37.9%] of 380). Sulfasalazine was the most common csDMARD administered (165 [42.4%] of 389 patients), followed by methotrexate (119 [30.6%] of 389 patients), while 87 patients (22.4%) were taking both drugs and 18 patients (4.6%) were taking another csDMARD. Compared to those not receiving csDMARDs, those receiving csDMARDs had higher mean CRP levels, had higher numbers of tender and swollen joints, and were more likely to be cotreated with oral steroids and NSAIDs (Table 1).

Table 1. Baseline characteristics of the patients discontinuing or not discontinuing TNFi and those receiving or not receiving csDMARD comedication during the follow-up*

	Patients with TNFi discontinuation (n = 289)	Patients without TNFi discontinuation (n = 665)	Patients with any csDMARD comedication (n = 389)†	Patients without csDMARD comedication (n = 565)
Age at disease onset, mean ± SD years (n = 822)	27.6 ± 11.1	27.8 ± 11.2	28.8 ± 11.3	27.1 ± 11.0
Disease duration, mean ± SD years (n = 822)	13.7 ± 10.6	13.6 ± 10.3	13.5 ± 10.4	13.8 ± 10.4
Age, mean ± SD years	41.0 ± 11.7	41.9 ± 12.2	42.5 ± 12.7	41.0 ± 11.6
Male sex, no. (%)	158 (54.7)	411 (61.8)	216 (55.5)	353 (62.5)
Years of formal education, mean ± SD	10.5 ± 4.7	10.0 ± 4.3	10.0 ± 4.5	10.4 ± 4.4
Current smoker, no. (%)	71 (29.8)	134 (26.4)	79 (23.9)	126 (30.4)
Number of painful joints (range 0–75), mean ± SD (n = 603)	4.5 ± 7.5	3.6 ± 6.0	5.5 ± 8.1	2.4 ± 4.2
Number of swollen joints (range 0–72), mean ± SD (n = 581)	1.0 ± 2.0	1.2 ± 2.2	1.7 ± 2.6	0.6 ± 1.5
At least 1 swollen joint, no. (%) (n = 581)	63 (34.8)	138 (34.5)	137 (48.8)	64 (21.3)
ESR, mean ± SD mm/hour (n = 614)	34.2 ± 25.4	34.9 ± 26.3	36.6 ± 26.5	33.0 ± 25.4
CRP, mean ± SD mg/dl (n = 613)	2.4 ± 3.4	2.5 ± 3.3	2.8 ± 3.4	2.1 ± 3.2
Patient's global assessment of disease activity on VAS (scale 0–100), mean ± SD (n = 616)	65.7 ± 22.9	63.4 ± 24.2	63.2 ± 24.8	65.0 ± 22.9
Patient's pain assessment on VAS (scale 0–100), mean ± SD (n = 585)	60.9 ± 23.5	57.8 ± 26.7	57.2 ± 27.1	60.2 ± 24.5
BASDAI (scale 0–10), mean ± SD (n = 633)	6.3 ± 1.8	5.9 ± 1.9	6.1 ± 2.0	6.0 ± 1.8
ASDAS				
Continuous score, mean ± SD (n = 560)	3.8 ± 1.0	3.7 ± 0.9	3.8 ± 0.99	3.7 ± 0.90
High or very high disease activity, no. (%) (n = 560)	177 (97.3)	365 (96.6)	253 (95.8)	289 (97.6)
BASFI (scale 0–10), mean ± SD (n = 564)	5.9 ± 2.3	5.5 ± 2.5	5.5 ± 2.5	5.8 ± 2.3
TNFi, no. (%)				
Adalimumab	80 (27.7)	205 (30.8)	115 (29.6)	174 (30.1)
Etanercept	69 (23.9)	211 (31.7)	117 (30.1)	163 (28.9)
Golimumab	27 (9.3)	105 (15.8)	102 (26.2)	155 (27.4)
Infliximab	113 (39.1)	144 (21.7)	55 (14.1)	77 (13.6)
Any csDMARD, no. (%)	121 (41.9)	268 (40.3)	NA	NA
Oral steroids, no. (%)	65 (22.5)	109 (16.4)	126 (32.4)	48 (8.5)
NSAIDs, no. (%)	119 (41.2)	223 (33.5)	167 (42.9)	175 (31.0)

* TNFi = tumor necrosis factor inhibitors; csDMARD = conventional synthetic disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; VAS = visual analog scale; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASFI = Bath Ankylosing Spondylitis Functional Index; NA = not applicable; NSAIDs = nonsteroidal antiinflammatory drugs.
† Methotrexate alone, n = 119; sulfasalazine alone, n = 165; sulfasalazine and methotrexate, n = 87; other, n = 18.

Reason for TNFi discontinuation and unadjusted drug survival. Of the 954 patients, 289 (30.3%) discontinued their first TNFi after a median follow-up time of 2.5 years (range 0.08–13 years). The annual discontinuation rate was 9.7% (95% confidence interval [95% CI] 8.6–10.9%), with a probability of maintaining the same TNFi after 1 year, 2 years, and 5 years of 81.5%, 76.3%, and 62.8%, respectively (Figure 1A).

As shown in Table 2, inefficacy was the most common reason for TNFi discontinuation (55.7% of patients), followed by adverse events (31.1% of patients). Allergic reactions and infections were the leading reasons for discontinuation due to adverse events (9.0% and 8.7%, respectively), but these were relatively uncommon when considering all reasons for discontinuation.

The annual rate of TNFi discontinuation was not significantly different between patients receiving csDMARDs at baseline and those not receiving csDMARDs. Specifically, between patients receiving csDMARD comedication and those not receiving csDMARD comedication, no significant differences were observed with regard to the rate of discontinuation due to any reason (9.9% versus 9.5%; $P = 0.79$), rate of discontinuation due to inefficacy (52.5% versus 49.1%; $P = 0.62$), or rate of discontinuation due to an adverse event (75.0% versus 67.3%; $P = 0.76$).

Baseline and time-varying predictors of TNFi discontinuation. Table 3 shows the multivariable models in which we tested the baseline and time-varying predictors of TNFi discontinuation. Comedication with csDMARDs had no effect on the rate of TNFi discontinuation, neither at baseline (hazard ratio [HR] 0.83, 95% CI 0.59–1.16) nor during follow-up in the model assessing it as a time-varying covariate (HR 1.07, 95% CI 0.68–1.68). In a subgroup analysis, we found that patients receiving methotrexate were significantly less likely to discontinue their first TNFi as compared to

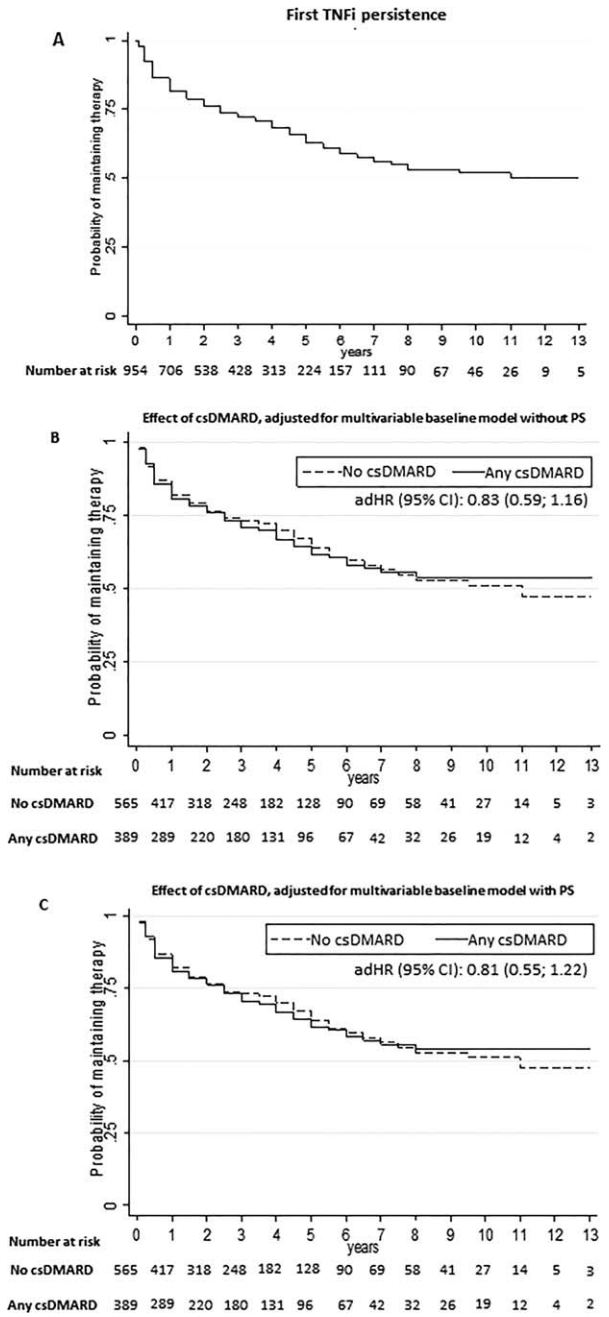

Figure 1. Unadjusted probability of maintaining treatment (drug survival) with the first tumor necrosis factor inhibitor (TNFi) in patients with spondyloarthritis. Drug survival over the follow-up period was assessed in all patients (**A**) and between patients who received conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and those who did not receive csDMARDs, adjusted for the baseline multivariable model without propensity score (PS) adjustment (**B**) or with propensity score adjustment (**C**). adHR = adjusted hazard ratio; 95% CI = 95% confidence interval.

those not receiving this drug, as determined in the baseline model (HR 0.60, 95% CI 0.41–0.89) but not in the model with time-varying covariates (HR 0.87, 95% CI 0.52–1.45). The effect of sulfasalazine on TNFi discontinuation was found to be nonsignificant, both in the baseline model (HR 1.00, 95% CI 0.73–1.40) and in the model with time-varying variables (HR 0.95, 95% CI 0.59–1.52).

In the baseline model with fixed covariates, an elevated CRP level was associated with TNFi retention (HR 0.62, 95% CI 0.46–0.84), and starting treatment with the TNFi after 2007 was associated with TNFi discontinuation (HR 1.81, 95% CI 1.19–2.75). Patients taking adalimumab and those taking etanercept had longer TNFi retention as compared to those taking infliximab (HR 0.65, 95% CI 0.45–0.95 and HR 0.55, 95% CI 0.38–0.80, respectively). We found no statistically significant interaction between csDMARD use at baseline and use of any of the different TNFi ($P = 0.86$), nor was there any statistically significant interaction between csDMARD use and the presence of peripheral arthritis, when the latter was defined as having at least 1 swollen joint ($P = 0.54$), at least 1 painful joint ($P = 0.16$), or both ($P = 0.43$). These interactions were also not significant when considering separately those patients taking methotrexate and those taking sulfasalazine (data not shown).

Table 2. Reasons for discontinuation of the first TNFi in patients with spondyloarthritis*

Inefficacy	161 (55.7)
Primary failure†	50 (17.3)
Secondary failure†	36 (12.5)
Adverse event	90 (31.1)
Allergy	26 (9.0)
Infection‡	25 (8.7)
Malignancy§	5 (1.7)
Liver dysfunction (except viral hepatitis)	5 (1.7)
Psoriasis	4 (1.4)
Hematologic disorders	3 (1.0)
Pulmonary diseases except infection¶	2 (0.7)
Not specified	12 (4.2)
Other adverse event	8 (2.8)
Other reason	27 (9.3)
Unknown reason	11 (3.8)
Total no. with TNFi discontinuation	289

* Values are the number (%) of patients (total cohort n = 954). TNFi = tumor necrosis factor inhibitor.
† Defined according to the Ankylosing Spondylitis Disease Activity Score showing clinically important improvement (a decrease from baseline of ≥1.1) at 3 months compared to baseline. A patient was classified in the primary failure group if a treatment response at 3 months was not achieved, and in the secondary failure group if a treatment response at 3 months was achieved but then was lost at any time during the follow-up before discontinuation. For 75 patients, who discontinued because of inefficacy as determined by the rheumatologist, no information regarding disease activity at 3 months was available.
‡ Includes 4 cases of active tuberculosis.
§ One case of prostate cancer, 1 case of carcinoid, 2 cases of breast cancer, and 1 case of endometrium carcinoma.
¶ Two cases of interstitial pneumonia.

Table 3. Baseline and time-varying determinants of first TNFi discontinuation as determined in multivariable Cox regression analyses*

	Baseline model, HR (95% CI) (n = 613)	Time-varying model, HR (95% CI) (n = 470)
Age at baseline (<40 years vs. ≥40 years)	0.57 (0.18–1.78)†	‡
Sex (male vs. female)	0.76 (0.57–1.02)†	0.62 (0.34–1.11)†
Years of formal education	§	1.05 (1.01–1.10)
TNFi start year (at or after 2007 vs. before 2007)	1.81 (1.19–2.75)	2.11 (1.19–3.71)
Elevated CRP level (relative to <0.5 mg/dl)	0.62 (0.46–0.84)	¶
BASDAI score (scale 0–10)	§	¶
ASDAS (scale 0–10)	#	2.09 (1.78–2.45)
Any csDMARD (relative to no csDMARDs)	0.83 (0.59–1.16)†	1.07 (0.68–1.68)†
TNFi (relative to infliximab)		
Adalimumab	0.65 (0.45–0.95)	0.83 (0.50–1.40)†
Etanercept	0.55 (0.38–0.80)	0.61 (0.36–1.02)†
Golimumab	0.78 (0.46–1.33)	0.95 (0.41–2.25)†

* Both models were adjusted for the pattern of conventional synthetic disease-modifying anitrheumatic drug (csDMARD) use (never, continued, stopped at beginning of tumor necrosis factor inhibitor [TNFi] treatment, began with TNFi treatment, began after TNFi treatment) and use of nonsteroidal antiinflammatory drugs and oral steroids. HR = hazard ratio; 95% CI = 95% confidence interval; CRP = C-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS = Ankylosing Spondylitis Disease Activity Score.
† Forced entry in the final model due to clinical relevance.
‡ Not included in the multivariable analysis to avoid overfitting the model (time variable also included). Other variables that were tested in the univariable analysis and not selected for the multivariable analysis ($P \geq 0.20$ in the univariable model) were age at disease onset, disease duration, and smoking status.
§ Not selected during multivariable analysis ($P \geq 0.05$). Other variables not selected in the multivariable analysis were the erythrocyte sedimentation rate, number of swollen joints, number of tender joints, patient's global assessment of disease activity on visual analog scale (VAS), patient's assessment of pain on VAS, and the Bath Ankylosing Spondylitis Functional Index.
¶ Not included because of collinearity.
# Not included in the multivariable model ($P \geq 0.20$ in the univariable model).

In the model with time-varying covariates during follow-up, an association with TNFi discontinuation was found in patients with more years of formal education (HR 1.05, 95% CI 1.01–1.10), those who started treatment with the TNFi after 2007 (HR 2.11, 95% CI 1.19–3.71), and those with a high ASDAS during follow-up (HR 2.09, 95% CI 1.78–2.45). In addition, in a separate model, a high BASDAI (HR 1.26, 95% CI 1.16–1.37) and elevated CRP levels (HR 2.41, 95% CI 1.64–3.55) were also independent time-varying determinants of TNFi discontinuation. We found a trend toward longer TNFi retention in men as compared to women, both in the baseline model (HR 0.76, 95% CI 0.57–1.02) and in the model with time-varying covariates (HR 0.62, 95% CI 0.34–1.11).

Results of sensitivity analysis. In models adjusted for the treatment propensity score, the treatment effect of csDMARD comedication on TNFi retention remained statistically nonsignificant, both in the baseline model (HR 0.81, 95% CI 0.55–1.22) (Table 4 and Figures 1B and C) and in the time-varying model (HR 0.99, 95% CI 0.57–1.74). Similarly, the significant effect

Table 4. Effect of csDMARD comedication on TNFi discontinuation at baseline and as a time-varying covariate, without and with propensity score adjustment*

	Baseline model, HR (95% CI)	Time-varying model, HR (95% CI)
Without propensity score adjustment†	0.83 (0.59–1.16)	1.07 (0.68–1.68)
With propensity score adjustment‡	0.81 (0.55–1.22)	0.99 (0.57–1.74)

* Values are the hazard ratio (HR) with 95% confidence interval (95% CI) for discontinuation of tumor necrosis factor inhibitors (TNFi) in patients receiving any conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) relative to those not receiving any csDMARDs.
† For the full models, see Table 3.
‡ Same baseline model and model with time-varying covariates as in Table 3, as well as the propensity score added as a covariate.

of methotrexate in the baseline model was lost after propensity score adjustment (HR 0.73, 95% CI 0.48–1.09) and remained nonsignificant in the model with time-varying variables (HR 1.03, 95% CI 0.55–1.91). Furthermore, the effect of sulfasalazine remained nonsignificant after propensity score adjustment in both models (HR 0.98, 95% CI 0.67–1.44 in the baseline model and HR 0.94, 95% CI 0.53–1.65 in the time-varying model).

DISCUSSION

In this nationwide prospective, observational study of patients with SpA, we demonstrate a high rate of long-term TNFi retention (63% of patients after 5 years), which may reflect an overall acceptable effectiveness in daily practice. Importantly, comedication with csDMARDs did not have a measurable effect on TNFi retention, neither in the prediction analysis (with baseline and time-varying covariates) nor in the dedicated propensity-adjusted analysis with a focus on confounding by indication.

Drug retention is a complex outcome measure that captures not only benefits but also potentially harmful effects of the treatment (e.g., adverse events, unacceptable costs, and lack or loss of efficacy) and is commonly used in observational research to assess the effectiveness of a drug in real world settings (6). Although highly relevant to clinical practice, the effect of csDMARD comedication on TNFi retention in patients with SpA has rarely been tested, and previous studies have yielded contradictory results; while some investigators have failed to find a benefit (8–10), others have demonstrated beneficial effects (11). However, the well-known methodologic challenges of observational research justify cautious interpretations of these reports, in which incomplete or fallible analyses may have led to spurious conclusions (12). With these challenges in mind, we sought to confirm whether csDMARDs prolong TNFi retention in patients with SpA in clinical practice.

In the current study, we assessed the association between csDMARD comedication and TNFi retention after adjusting for a comprehensive set of potential patient- and disease-related confounders. Moreover, unlike previous studies, besides controlling for baseline covariates, we also estimated the treatment effect of csDMARDs as a time-varying variable, in models adjusted for covariates that change over time (e.g., 6-monthly repeated measures of disease activity). While the baseline model provides the prognostic effect of these features at the start of therapy, the model with time-varying variables accounts for their dynamic changes and how these variations influence TNFi retention after treatment start. In this prediction analysis, no effect of comedication with csDMARDs, neither at baseline nor during therapy, was observed. On the contrary, high disease activity had significant, but opposite, effects between baseline (TNFi retention) and follow-up (TNFi discontinuation). These seemingly discrepant results truly reflect different domains; that is, whereas at baseline, high disease activity is prognostic for a higher treatment response and, thus, may favor TNFi retention, during follow-up, time-varying disease activity measures are indicators of treatment failure (physicians tend to stop the TNFi treatment in patients with persistently high disease activity). Therefore, it is important to adjust for repeated measures of disease activity, as well as other time-varying covariates, to best estimate the treatment effect of csDMARDs, rather than to consider only the baseline values (as has been done thus far).

Despite this comprehensive set of adjustments, the nonsignificant effect of csDMARDs on TNFi retention estimated in the prediction analysis may still be blurred by selection bias, in particular by a specific type of selection bias, appropriately labeled confounding by indication (or channeling bias) (13,28). Unlike in RCTs, in which random treatment allocation ensures that differences in outcomes between the treated and untreated patients are not affected (or confounded) by the patients' characteristics prior to treatment (14), in our study (as in any observational study), the patient's baseline characteristics are expected to have an effect. In fact, rheumatologists may have preferentially prescribed csDMARDs to patients with more active/severe disease (as suggested by the higher CRP levels and higher numbers of tender and swollen joints at baseline among those taking csDMARDs). By definition, a confounding factor (such as disease activity) is associated with both the exposure (csDMARDs) and the outcome (TNFi discontinuation). Therefore, the effect of csDMARDs on TNFi retention may represent a mixing of effects that is driven by prognostic dissimilarities between csDMARD users and nonusers, thus hindering a direct assessment of the true treatment effect (29).

Although it has been shown that confounding by indication cannot be appropriately handled by simple covariate adjustment, propensity score adjustment can effectively control for this type of selection bias (14). To our knowledge, this is the first study to evaluate the propensity score–adjusted effect of csDMARDs on TNFi retention in patients with SpA. With propensity score adjustment, variables that affect treatment assignment, such as the presence of peripheral arthritis, were balanced between csDMARD users and nonusers

(pseudo-randomization). Our results indicate that TNFi retention was still independent of the use of csDMARD comedication, even after the analyses were controlled for confounding by indication, by considering patients receiving any csDMARD and also considering separately those patients receiving either methotrexate or sulfasalazine.

The longer TNFi retention among patients receiving etanercept and those receiving adalimumab as compared to those receiving infliximab may also be affected by confounding by indication. Thus, our results pertaining to differences between the various TNFi retention rates must be carefully interpreted. The current study did not aim to address this question and, unlike the effect of csDMARDs on TNFi retention, confounding by indication was not corrected for this association.

In addition to measures of disease activity (the ASDAS, CRP level, and BASDAI) and a modest effect of education, no other patient- and disease-related features (neither time-fixed nor time-varying) were found to be predictors of TNFi retention. Although previous studies have also identified other predictors of TNFi retention, such as younger age and male sex, these variables were not consistently significant across the studies (8,10,15–18). This shows that we are not yet able to identify those patients who will most likely benefit from TNFi therapy. More research on additional biomarkers with prognostic value is warranted (30).

Our study has several strengths, but also limitations. This was a large nationwide study performed in a real world setting, rendering its results easy to translate into daily practice. Moreover, we utilized the most comprehensive set of adjustments yet performed to handle confounding of the effect of csDMARDs on TNFi retention, including, to the extent possible, confounding by indication. However, the possibility of residual confounding from unmeasured variables can never be completely ruled out. In addition, we have also addressed information bias by completing the information in the central database with data from local medical records. Even so, missing data on features of the patients with SpA precluded assessment of the patients' disease classification status according to the ASAS SpA criteria. However, cases of SpA were defined on the basis of the treating rheumatologist's diagnosis, which is commonly done in registry studies to best reflect clinical practice.

In conclusion, after adjustment for potential time-fixed and time-varying confounders and controlling for confounding by indication, csDMARD comedication did not protect against discontinuation of the first TNFi in patients with SpA in clinical practice. Our results suggest that there is no added benefit from concomitant use of these drugs in patients with SpA.

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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 published. Dr. Sepriano 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.

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REFERENCES

1. Callhoff J, Sieper J, Weiß A, Zink A, Listing J. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis 2015;74:1241–8.
2. Sieper J. Developments in therapies for spondyloarthritis. Nat Rev Rheumatol 2012;8:280–7.
3. Davis JC Jr, van der Heijde DM, Dougados M, Braun J, Cush JJ, Clegg DO, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. J Rheumatol 2005;32:1751–4.
4. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDI 50) to tumour necrosis factor α blockers in ankylosing spondylitis. Ann Rheum Dis 2004; 63:665–70.
5. Rudwaleit M, Claudepierre P, Wordsworth P, Cortina EL, Sieper J, Kron M, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. J Rheumatol 2009;36:801–8.
6. Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol 1995;9:619–32.
7. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices. Part II. Second line drugs and prednisone. J Rheumatol 1992;19: 1885–94.
8. Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO Registry. Ann Rheum Dis 2010;69:2002–8.
9. Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti–tumor necrosis factor α drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 2008;59:234–40.
10. Kristensen LE, Karlsson JA, Englund M, Petersson IF, Saxne T, Geborek P. Presence of peripheral arthritis and male sex predicting continuation of anti–tumor necrosis factor therapy in

ankylosing spondylitis: an observational prospective cohort study from the South Swedish Arthritis Treatment Group Register. Arthritis Care Res (Hoboken) 2010;62:1362–9.
11. Lie E, Kristensen LE, Forsblad-d'Elia H, Zverkova-Sandstrom T, Askling J, Jacobsson LT, et al. The effect of comedication with conventional synthetic disease modifying antirheumatic drugs on TNF inhibitor drug survival in patients with ankylosing spondylitis and undifferentiated spondyloarthritis: results from a nationwide prospective study. Ann Rheum Dis 2015;74:970–8.
12. Landewe RB. Conventional DMARDs in axial spondyloarthritis: wishful–rather than rational–thinking! Ann Rheum Dis 2015;74: 951–3.
13. Landewe RB. Methotrexate saves lives: a pearl of observational research. Arthritis Rheum 2013;65:307–9.
14. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.
15. Arends S, Brouwer E, van der Veer E, Groen H, Leijsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-α blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther 2011;13:R94.
16. Busquets N, Tomero E, Descalzo MA, Ponce A, Ortiz-Santamaria V, Suris X, et al. Age at treatment predicts reason for discontinuation of TNF antagonists: data from the BIOBADASER 2.0 Registry. Rheumatology (Oxford) 2011;50:1999–2004.
17. Luc M, Gossec L, Ruyssen-Witrand A, Salliot C, Duclos M, Guignard S, et al. C-reactive protein predicts tumor necrosis factor-α blocker retention rate in axial ankylosing spondylitis. J Rheumatol 2007;34:2078–81.
18. Gulfe A, Kapetanovic MC, Kristensen LE. Efficacy and drug survival of anti-tumour necrosis factor-α therapies in patients with non-radiographic axial spondyloarthritis: an observational cohort study from Southern Sweden. Scand J Rheumatol 2014;43:493–7.
19. Carmona L, Gomez-Reino JJ, BIOBADASER Group. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis: data from the Spanish registry BIOBADASER. Arthritis Res Ther 2006;8:R72.
20. Duclos M, Gossec L, Ruyssen-Witrand A, Salliot C, Luc M, Guignard S, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33:2433–8.
21. Canhao H, Faustino A, Martins F, Fonseca JE. Reuma.pt: the Rheumatic Diseases Portuguese Register. Acta Reumatol Port 2011;36:45–56.
22. Van der Meulen JH, Jacob M, Copley L. Assessing the quality of the data in a transplant registry: the European Liver Transplant Registry. Transplantation 2003;75:2164–7.
23. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.
24. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
25. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
26. Sieper J, Rudwaleit M, Braun J. Adalimumab for the treatment of ankylosing spondylitis. Expert Opin Pharmacother 2007;8:831–8.
27. Hertz-Picciotto I, Rockhill B. Validity and efficiency of approximation methods for tied survival times in Cox regression. Biometrics 1997;53:1151–6.
28. Schwartz S, Campbell UB, Gatto NM, Gordon K. Toward a clarification of the taxonomy of "bias" in epidemiology textbooks. Epidemiology 2015;26:216–22.
29. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002;359:248–52.
30. Maksymowych WP. Biomarkers in axial spondyloarthritis. Curr Opin Rheumatol 2015;27:343–8.