

EXTENDED REPORT

Comparative effectiveness of biologic monotherapy versus combination therapy for patients with psoriatic arthritis: results from the Corrona registry

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ABSTRACT

Objectives: To characterise the comparative effectiveness of combination therapy (a tumour necrosis factor inhibitor (TNFi) and a conventional synthetic disease-modifying antirheumatic drug (csDMARD) such as methotrexate) and monotherapy (TNFi only) for psoriatic arthritis (PsA) from a large US registry.

Methods: The analysis included adult patients with PsA who were enrolled in the Corrona database (ClinicalTrials.gov, NCT01402661), had initiated a TNFi, were biologic naïve, and had a follow-up visit ≥ 90 days after drug initiation. The endpoints of the analysis were TNFi persistence (drug survival) and time to Clinical Disease Activity Index (CDAI) remission. All analyses were performed using propensity scoring, which were estimated using CDAI and patient sex, to control for channelling bias.

Results: Of 519 patients meeting the inclusion criteria (318 with combination therapy and 201 with monotherapy), the analysis population was 497 for TNFi persistence and 380 for time to remission. The difference between combination therapy (TNFi +methotrexate, 91% of patients; TNFi+other csDMARD, 9%) and monotherapy was not statistically significant for TNFi persistence (32 and 31 months, $p=0.73$) and time to remission (21 and 25 months, $p=0.56$). Predictors of TNFi persistence included Hispanic ethnicity (longer persistence), PsA duration (longer persistence), history of methotrexate use (shorter persistence), body mass index (shorter persistence) and disease activity (shorter persistence).

Conclusions: Patients with PsA from a large US registry experienced similar TNFi persistence on combination therapy and monotherapy. Prospective, randomised clinical trials evaluating the efficacy of combination therapy versus monotherapy would provide much-needed clarity on treatment options for patients with PsA.

Trial registration number: NCT01402661.

Key messages**What is already known about this subject?**

► There is conflicting evidence about the clinical effectiveness of tumour necrosis factor inhibitor (TNFi) monotherapy versus combination therapy (ie, with a conventional synthetic disease-modifying antirheumatic drug such as methotrexate) in psoriatic arthritis. We performed an analysis of TNFi persistence (ie, time to therapy change) in a large, US-based, prospective registry.

What does this study add?

► We performed an analysis of TNFi persistence (ie, time to therapy change) in a large, US-based, prospective registry.
► There was no statistically significant difference in TNFi persistence between patients using monotherapy and combination therapy (32 and 31 months) or time to remission (21 and 25 months).

How might this impact on clinical practice?

► Our analysis indicates that TNFi persistence is similar between monotherapy and combination therapy, a result that is consistent with similar analyses of registries from other countries.
► Clinical trials should be conducted to verify the findings of this and other observational registries.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease that occurs in approximately 0.3% of the US population, as suggested by previous studies.^{1 2} However, it has recently been shown that up to 30% of patients with psoriasis may have PsA,³ and recent population surveys show that psoriasis occurs in 3.2% of the US population.⁴ Therefore,

previous estimates of PsA general population prevalence may underestimate the true prevalence. Early intervention is important, because the persistent inflammation can cause progressive joint damage leading to physical limitations and severe disability in some patients.^{5 6} In addition, PsA can increase the risk for cardiovascular complications and death.⁷⁻⁹ Therefore, optimal treatment strategies are important to understand.

Treatment strategies for patients with moderate to severe PsA have historically been based on extrapolation of efficacy data from patients with rheumatoid arthritis (RA). Like in RA, tumour necrosis factor (TNF)- α plays a key role in the pathogenesis of PsA, and a number of clinical trials have shown that TNF inhibitors (TNFis) are effective in patients with PsA.¹⁰⁻¹⁴ Coadministration of a conventional synthetic disease-modifying antirheumatic drug (csDMARD), such as methotrexate (MTX), improves the efficacy of TNFis in the treatment of RA^{15 16}; therefore, combination therapy is commonly used to treat PsA.^{17 18} PsA is, however, distinct from RA with respect to its pathology, clinical characteristics and outcomes,^{5 17 19 20} and no randomised controlled clinical trials have prospectively compared the effectiveness of combination therapy versus monotherapy in PsA.

The phase 3 studies of TNFis in PsA allowed patients receiving MTX at time of enrolment to continue MTX, and similar clinical responses were observed among patients who received concomitant MTX therapy versus those who received TNFi as monotherapy.¹⁰⁻¹⁴ A number of observational studies of real-world registry data found that higher percentages of patients with PsA receive MTX in combination with a TNFi versus a TNFi alone.²¹⁻²³ An analysis of PsA data from the South Swedish Arthritis Treatment Group (SSATG) register showed that concomitant MTX did not affect treatment responses.²² Likewise, the Norwegian DMARD (NOR-DMARD) study found no benefit of concomitant MTX.²¹ There was a small beneficial effect of concomitant MTX on the achievement of American College of Rheumatology 20% (ACR20) response among patients enrolled in the Danish Biologics (DANBIO) registry.²³ The effect of concomitant MTX on drug survival varied among the three registry studies, with a trend towards longer drug survival in the SSATG study²² and the DANBIO study (significant after the analysis was adjusted for other baseline variables)²³ and significantly longer drug survival in the NOR-DMARD study.²¹

There is variable evidence regarding the effectiveness of combination therapy versus monotherapy in PsA. Moreover, MTX is the most widely used systemic agent for PsA, whether used alone or in combination with a biologic. The data to date, which include two neutral placebo-controlled studies^{24 25} and some positive open-label studies, indicate that MTX modifies symptoms but not the underlying disease.²⁶ Clinicians must make individualised decisions about whether to prescribe MTX with a biologic in PsA, so we performed a study to provide more data on the comparative effectiveness of

combination therapy and monotherapy. The objectives of our study were to examine the effects of these treatment regimens on TNFi persistence (termed drug survival in other studies) and measures of effectiveness using a large, US-based registry: the Corrona registry (ClinicalTrials.gov, NCT01402661). We also investigated predictors of TNFi persistence and treatment response.

METHODS

Data source

Corrona is a large, US-based, independent, prospective, observational, disease-based registry initiated in 2001 that has always collected data on patients with RA and PsA. Patients are enrolled in the registry by participating rheumatologists, and questionnaires are completed by both patients and physicians during the visits as part of routine clinical care. Corrona is a prospective observational registry where data collection is not mandated at regular intervals. Physicians are encouraged to complete the questionnaires at least every 6 months (mean interval for current study, 8.6 \pm 5.4 months). Corrona is reviewed by the New England Institutional Review Board.

The analysis was performed on data collected between 2005 and 1 October 2012. During that time Corrona had enrolled 5408 adult patients with PsA, comprising 25 865 visits to 54 rheumatologists from 84 sites in 33 states. The mean \pm SD follow-up for these patients was 2.1 \pm 2.2 years (range 0-7.72 years; total of 11 550 patient-years).

Study population

Patients were included in the analysis if they had a diagnosis of PsA; were at least 18 years old; initiated a biologic in 2005 or later, either alone or in combination with a csDMARD; were biologic naïve; and had a follow-up visit at least 90 days after drug initiation. The diagnosis of PsA was according to the physician's designation on the form; the registry existed before the Classification criteria for Psoriatic ARthritis (CASPAR) criteria were published in 2006.²⁷ For the analysis of TNFi persistence, patients had a follow-up visit of at least 1 year after drug initiation.

Study objectives

The objectives of the analysis were to estimate effectiveness measured by the length of time that patients with PsA maintained their initial biologic therapy (TNFi persistence), either as monotherapy or in combination with MTX or other csDMARDs (an a priori comparison); time to remission; and effects of patient risk factors on these outcomes.

Change in monotherapy was defined as any change in the initial biologic, including the addition of a csDMARD or changing or stopping the biologic. Change in combination therapy was defined as changing or

stopping the biologic. Remission was defined as a Clinical Disease Activity Index (CDAI) score <2.8 .

Baseline disease activity

Measurements of baseline disease activity included CDAI, physician global assessment of disease activity and skin, patient global assessment of disease activity and skin, modified Health Assessment Questionnaire (mHAQ), tender and swollen joint counts, erythrocyte sedimentation rate levels, and levels of C reactive protein (CRP).

Statistical analyses

The data sets used in the analyses are shown in [figure 1](#). Patients initiating a non-TNFi biologic were excluded from the analysis owing to the small number of patients (n=12).

TNFi persistence (measured as the time from the date of initiation of biologic therapy to the date of change in therapy) was estimated using the Kaplan–Meier method. Kaplan–Meier curves were estimated for the monotherapy and combination therapy groups, as well as the individual TNFis. Log-rank tests were used to compare the monotherapy and combination therapy groups. The Kaplan–Meier method was also used to estimate the median time to therapy change and the proportion of patients who remained on their initial biologic therapy at different follow-up time points.

To control for channelling bias, all patients receiving monotherapy or combination therapy were matched using a propensity score matching method.^{28 29} The propensity score was estimated using CDAI and patient sex. These variables were chosen following an analysis of the data using other possible risk factors (swollen and tender joint counts, CDAI, physician global assessment of disease activity, history of csDMARD use and history of MTX use). CDAI has correlated with many other disease severity measures. Therefore, we felt CDAI would be a good indicator to represent overall disease activity at baseline, which we wanted to balance between the monotherapy and combination therapy groups. We also included patient sex in the model, because we have observed more women initiating combination therapy compared with men. In order to minimise the propensity score missingness due to missing covariates, we limited the covariates to CDAI and gender in the propensity score calculation.

We derived propensity scores for matching patients in the monotherapy and combination therapy groups based on the conditional probability of receiving either treatment. Weights were also constructed using propensity scores from logistic models and were normalised using inverse probability treatment weighting, rather than directly matching the monotherapy and combination therapy groups. Weights information was taken into account in proportional hazards regression models. A separate propensity score was calculated for each analysis of TNFi persistence by TNFi.

Patients who remained on their initial biologic therapy for at least 90 days were included in the analysis of time to remission.

Both univariate and multivariate Cox regression models were used to identify predictors of TNFi persistence and time to remission. In order to control the residual confounding effects after inverse probability treatment weighting, we adjusted covariates that were significant in the univariate models. Age and patient sex were not always significant in univariate analysis, but these variables were always included in multivariate models to adjust potential confounding or risk modification effects. Body mass index (BMI) was not always significant in univariate regression, but it was included in the multivariate model because it is an important clinical risk factor. Race and ethnicity variables were sometimes significant in the univariate model but were no longer significant after adjusting for other variables; therefore, these were not included in the multivariate model. We did not use a strict stay criterion for identifying predictors in the multivariate model; predictors were included in the multivariate model if they were marginally significant in the univariate model ($p < 0.10$), clinically important, or strongly prognostic.

All analyses were done using SAS V.9.1 (SAS Institute Inc, Cary, North Carolina, USA) and Stata V.10.1 (Stata Corp, College Station, Texas, USA). p Values <0.05 were considered statistically significant.

RESULTS

Baseline demographics, disease characteristics and medical history

A total of 519 patients (combination therapy, n=318; monotherapy, n=201) met the inclusion criteria ([table 1](#)). Most patients were white; approximately half were women; and the mean age was 51.6 years. Patient demographics and treatment history were similar between the

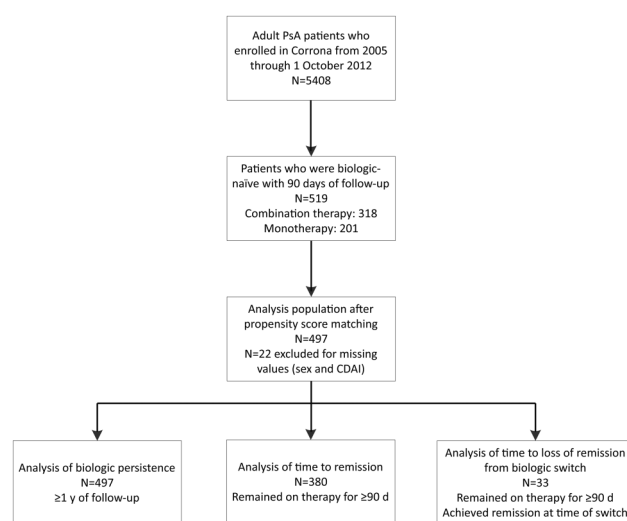


Figure 1 Data sets used in the analyses (CDAI, Clinical Disease Activity Index; PsA, psoriatic arthritis).

Table 1 Characteristics of patients with PsA in the longitudinal cohort of patients registered in the Corrona database

Patient characteristic	Total (N=519)	Combination therapy (N=318)	Monotherapy (N=201)	p Value
Female sex, n (%)	266 (51.4)	181 (57.1)	85 (42.3)	0.001
Age, mean (SD), years	51.6 (13.0)	52.0 (12.6)	51.0 (13.5)	0.38
BMI, mean (SD), kg/m ²	31.4 (7.1)	31.9 (7.4)	30.7 (6.5)	0.052
Race and ethnicity, n (%)				
White	495 (95.4)	303 (95.3)	192 (95.5)	0.95
Hispanic	21 (4.0)	9 (2.8)	12 (6.0)	0.22
Black	11 (2.1)	7 (2.2)	4 (2.0)	>0.99
Asian	9 (1.7)	6 (1.9)	3 (1.5)	>0.99
American Indian/Alaskan Native	6 (1.2)	3 (0.9)	3 (1.5)	0.68
Native Hawaiian/Pacific Islander	1 (0.2)	1 (0.3)	0 (0.0)	0.64
Other	3 (0.6)	2 (0.6)	1 (0.5)	>0.99
Marital status, n (%)				0.48
Married	358 (69.0)	223 (70.1)	135 (67.2)	
Single	85 (16.4)	47 (14.8)	38 (18.9)	
Divorced	38 (7.3)	20 (6.3)	18 (9.0)	
Other	38 (7.3)	28 (8.8)	10 (5.0)	
Education*				0.36
Primary	20 (3.9)	13 (4.1)	7 (3.5)	
High school	171 (32.9)	113 (35.5)	58 (28.9)	
College/university	313 (60.3)	185 (58.2)	128 (67.3)	
Not available	15 (2.9)	7 (2.2)	8 (4.0)	
Initiated TNFi, †n (%)				0.02
Adalimumab	218 (42.0)	130 (40.9)	88 (43.8)	
Etanercept	168 (32.4)	92 (28.9)	76 (37.8)	
Infliximab	114 (22.0)	83 (26.1)	31 (15.4)	
Other	19 (3.7)	13 (4.1)	6 (3.0)	
MTX use (history)	423 (81.5)	286 (89.9)	137 (68.2)	<0.001
PsA duration, mean (SD), years	6.3 (7.4)	6.4 (7.5)	6.2 (7.2)	0.84
Tender joint count, mean (SD)	3.3 (5.3)	3.7 (5.6)	2.6 (4.6)	0.02
Swollen joint count, mean (SD)	3.0 (4.8)	3.5 (5.3)	2.2 (3.8)	0.001
CDAI, mean (SD)	11.4 (10.8)	12.5 (11.1)	9.6 (9.9)	0.003
mHAQ, mean (SD)	0.32 (0.39)	0.34 (0.39)	0.29 (0.40)	0.20
Physician's global assessment, mean (SD)‡	20.1 (18.6)	21.5 (18.4)	18.0 (18.7)	0.04
Patient global assessment, mean (SD)‡	31.4 (25.8)	32.2 (25.1)	30.1 (27.0)	0.38
Physician's global assessment of skin, mean (SD)§‡	19.3 (23.5)	20.5 (24.7)	17.4 (21.2)	0.22
Patient's global assessment of skin, mean (SD)§‡	21.5 (24.2)	20.7 (23.5)	23.0 (25.5)	0.44
CRP, mean (SD),§ mg/L	8.4 (18.7)	8.2 (16.1)	8.9 (22.7)	0.83
ESR, mean (SD), mm/h	16.0 (17.7)	16.0 (16.7)	16.1 (19.3)	0.97
Any alcohol use, n (%)	277 (53.4)	152 (47.8)	125 (62.2)	0.001
Smoking status, n (%)				0.43
Never	272 (52.4)	168 (52.8)	104 (51.7)	
Previous	164 (31.6)	95 (29.9)	69 (34.3)	
Current	83 (16.0)	55 (17.3)	28 (13.9)	
History of hypertension, n (%)	139 (26.8)	82 (25.8)	57 (28.4)	0.52
History of diabetes, n (%)	49 (9.4)	36 (11.3)	13 (6.5)	0.06
Coronary artery disease (history),§ n (%)	18 (3.5)	11 (3.5)	7 (3.5)	0.98

*Highest education level received.

†May not total 100%; other biologics were excluded because of the small number of patients.

‡Visual analogue scale of 100 mm with higher values indicating greater disease worse disease activity/skin symptoms.

§Many forms did not record this variable.

BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; PSA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor.

two groups, except that almost twice as many patients in the combination therapy group had initiated treatment with infliximab (table 1). Patients in the combination

therapy group had significantly higher baseline tender and swollen joint counts, CDAI values, and physician's assessment of skin values than those in the monotherapy

Table 2 TNFi persistence, time to remission and time to loss of remission

	Combination therapy	Monotherapy
TNFi persistence, overall (n=497)		
Median (IQR), months	32.4 (12.0–NA)	30.8 (13.7–67.1)
HR (95% CI)	0.95 (0.70 to 1.29)	
p Value	0.73	
TNFi persistence, adalimumab (n=214)		
Median (IQR), months	29.5 (12.4–NA)	29.1 (11.9–47.1)
HR (95% CI)	0.88 (0.54 to 1.44)	
p Value	0.61	
TNFi persistence, etanercept (n=155)		
Median (IQR), months	19.1 (8.4–42.0)	47.3 (19.3–71.6)
HR (95% CI)	1.93 (1.15 to 3.25)	
p Value	0.01	
TNFi persistence, infliximab (n=110)		
Median (IQR), months	NA (22.0–NA)	16.3 (13.6–58.9)
HR (95% CI)	0.46 (0.24 to 0.88)	
p Value	0.02	
Time to remission* (n=380)		
Median (IQR), months	20.7 (7.4–58.5)	25.1 (8.1–64.6)
HR (95% CI)	1.09 (0.82 to 1.46)	
p Value	0.56	
Time to loss of remission† (n=33)		
Median (IQR), months	9.3 (7.0–20.7)	12.0 (7.8–NA)
HR (95% CI)	1.52 (0.63 to 3.68)	
p Value	0.35	

HR and p value relative to TNFi monotherapy.

*Patients with at least 90 days of initial therapy. TNFi, only biologic in both groups.

†Patients with at least 90 days of initial therapy and who had remission on the first therapy switch. TNFi, only biologic in both groups.

NA, not available; TNFi, tumour necrosis factor inhibitor.

group (table 1). Combination therapy included MTX for 91% of patients and another csDMARD, such as sulfasalazine or leflunomide, for 9%. The number of patients with valid propensity scores and weights in each analysis was 497 for TNFi persistence and 380 for time to remission (figure 1).

At baseline, 218 patients were taking adalimumab, 158 etanercept and 114 infliximab. Most baseline characteristics within each individual TNFi subgroup were balanced between the combination therapy and monotherapy groups. There was a greater proportion of patients with a history of MTX use in the combination therapy group in each individual TNFi subgroup. Compared to monotherapy, combination therapy was associated with a smaller proportion of women (etanercept only) and patients with alcohol use (adalimumab and etanercept), longer PsA duration (infliximab only),

and higher swollen joint count and erythrocyte sedimentation rate (infliximab only).

TNFi persistence

The difference in TNFi persistence between the combination therapy and monotherapy groups of all TNFis was not statistically significant (32.4 vs 30.8 months, $p=0.73$; table 2 and figure 2A). Considering individual TNFis, TNFi persistence between combination therapy and monotherapy favoured monotherapy with etanercept, was similar between therapies with adalimumab, and favoured combination therapy with infliximab (table 2 and figure 2B–D).

A number of predictors of TNFi persistence were identified for patients receiving combination therapy versus monotherapy (table 3). Hispanic ethnicity (not recorded for a substantial number of patients) and longer PsA duration were significant predictors of longer TNFi persistence in the univariate analysis. A history of prior treatment with MTX, history of coronary artery disease, higher BMI, and most measures of baseline disability and disease activity were significant predictors of shorter TNFi persistence in the univariate analysis. Higher mHAQ and CDAI scores were the only significant predictors (shorter TNFi persistence) in the multivariate analysis (table 3).

Achievement of remission

There was no statistically significant difference between the combination and monotherapy groups in median time to achieve remission (20.7 vs 25.1 months; $p=0.56$; table 2 and figure 3). A number of factors were significant predictors of a longer time to achieving remission in the univariate analysis, including female sex, higher BMI, higher baseline disability and disease activity, and history of hypertension or diabetes (table 3). Higher BMI and mHAQ score were the only significant predictors (longer time to achieving remission) in the multivariate analysis (table 3).

DISCUSSION

In a propensity score-matched analysis of patients with PsA who were enrolled in a large US-based registry, combination therapy of TNFi and csDMARD was not significantly different compared with TNFi monotherapy in TNFi persistence or time to remission. When the TNFi persistence analysis was stratified by TNFi, TNFi persistence was significantly longer with combination therapy in patients treated with infliximab, whereas it was either the same with both therapeutic approaches (adalimumab) or longer with monotherapy (etanercept) with the other TNFis. There was no difference between monotherapy and combination therapy in time to remission. Further analysis found significant predictors for shorter/longer TNFi persistence and time to achieving remission.

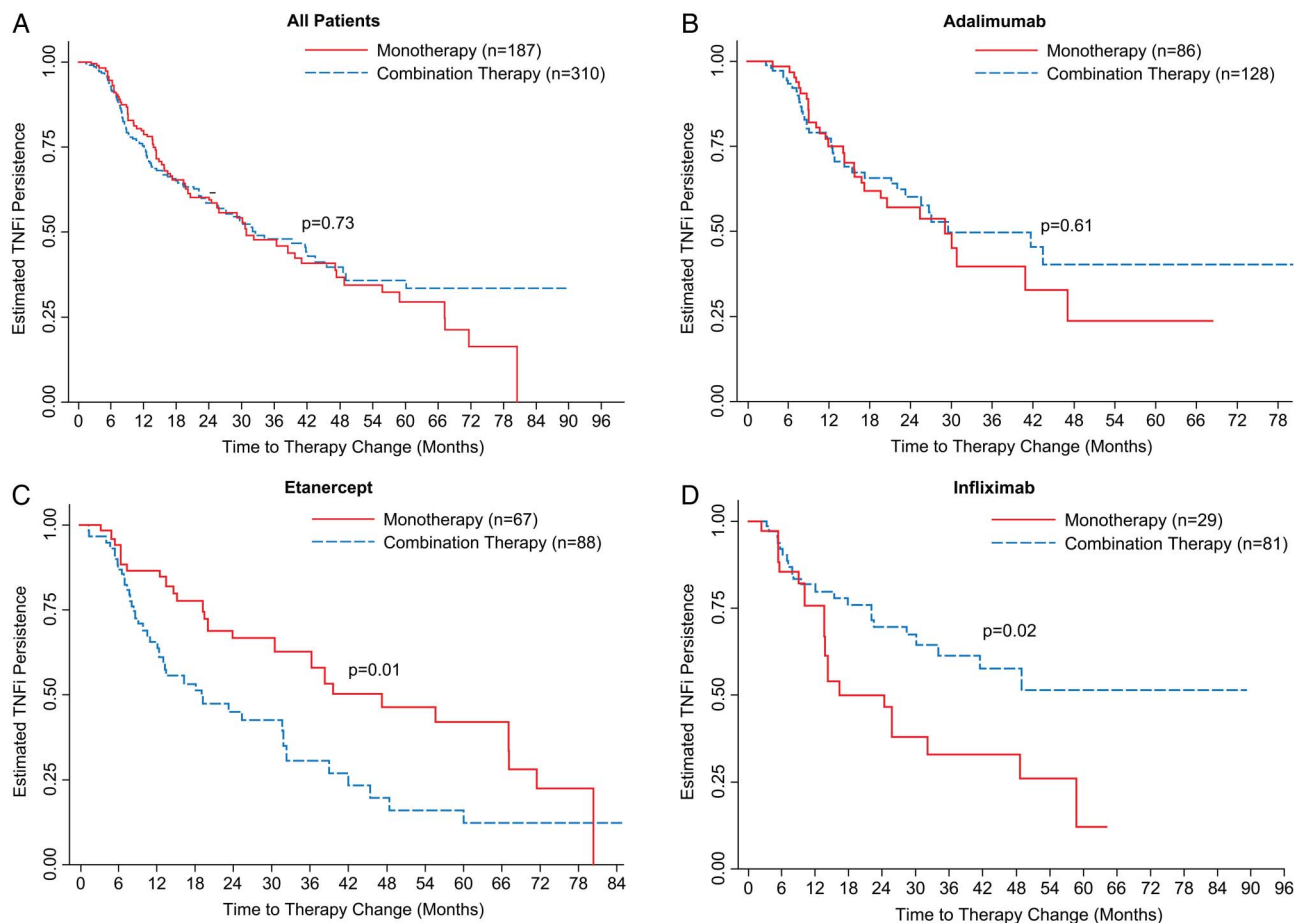


Figure 2 Time to change in initial tumour necrosis factor inhibitor (TNFi) therapy (ie, TNFi persistence) among (A) all patients and those taking (B) adalimumab, (C) etanercept and (D) infliximab. Patients were censored at their last follow-up visit if no change in therapy was observed.

Our results are similar to those of previous analyses of SSATG²² and DANBIO,²³ although in the latter, longer TNFi persistence was noted with combination therapy after adjustment for baseline variables. A NOR-DMARD analysis likewise found significantly longer TNFi persistence with combination therapy at years 1 and 2.²¹ A possible explanation for these differing results between registry studies may be due to differing contributions of individual TNFis, which have different efficacy profiles in PsA with or without a concomitant DMARD. In our analysis, by initial TNFi, we found that TNFi persistence was longer in monotherapy with etanercept, equivalent between therapeutic approaches with adalimumab, and longer in combination therapy with infliximab. These individualised results are mostly consistent with the NOR-DMARD study, which found equivalent TNFi persistence between monotherapy and combination therapy with etanercept and adalimumab and a difference favouring combination therapy with infliximab.²¹ The results by TNFi in our analysis and those of NOR-DMARD suggest that combination therapy in PsA has little effect on TNFi persistence compared with monotherapy with etanercept and adalimumab, whereas patients taking infliximab may experience significant

benefit by also taking a csDMARD such as MTX. Phase 3 studies of infliximab, etanercept and adalimumab for PsA stratified patients according to baseline MTX use in the treatment and placebo groups.^{10–12} The presence or absence of background MTX had no effect on therapeutic response, but because the enrolled patients were not having adequate response to MTX, these trials do not provide adequate evidence for assessing the potential role of combination MTX in PsA for any of the TNFis. The superiority of combination therapy to monotherapy for TNFis in RA, however, is well established.^{15 16 30 31} The RA indication for infliximab recommends concomitant MTX use to prevent loss of efficacy.³⁰ The exact mechanism of action for increased efficacy of combination therapy for all TNFis in RA and for infliximab combination therapy in PsA is not clear. It is known that MTX increases infliximab and adalimumab drug levels.^{30 32} Analyses of TNFis in RA have indicated that immunogenicity may play a role in reduced drug levels and efficacy,^{33–35} and some evidence is emerging that a similar phenomenon may occur in PsA.^{36–38} A recent study has suggested that antidrug antibodies are inversely associated with red blood cell MTX polyglutamates and that the latter are positively correlated with

Table 3 Univariate and multivariate analyses of predictors for TNFi persistence and time to remission

Variable	TNFi persistence				Time to remission			
	Univariate (n=497)		Multivariate (n=495)		Univariate (n=380)		Multivariate (n=379)	
	HR	p Value	HR	p Value	HR	p Value	HR	p Value
Used multivariate analysis								
Age, years	1.000	0.99	0.997	0.66	0.991	0.11	0.999	0.86
Sex, female vs male	1.279	0.13	1.256	0.18	0.744	0.046	0.826	0.21
Initial therapy, combination vs monotherapy	0.948	0.73	0.956	0.78	1.090	0.56	1.153	0.35
BMI, kg/m ²	1.030	0.01	1.011	0.44	0.940	<0.001	0.955	<0.001
CDAI, point value	1.037	<0.001	1.027	0.001	0.944	0.002	0.964	0.052
mHAQ, point value	2.307	<0.001	1.585	0.049	0.257	<0.001	0.478	0.008
PsA duration, years	0.978	0.04	0.982	0.10	0.999	0.93	0.997	0.77
Alcohol use, yes vs no	0.913	0.57	1.013	0.97	1.265	0.11	0.953	0.76
Smoking, ever vs never			1.015	0.89			0.851	0.14
Univariate: demographics								
Ethnicity, Hispanic vs non-Hispanic*	0.259	0.003			0.777	0.44		
Univariate: disease activity or disability								
Swollen joints, number	1.042	0.034			0.944	0.01		
Tender joints, number	1.084	<0.001			0.912	0.01		
Physician global assessment of disease activity, point value	1.016	0.001			0.978	0.001		
Patient global assessment of disease activity, point value	1.011	0.001			0.976	<0.001		
Physician global assessment of skin, point value*	1.006	0.12			0.981	<0.001		
Patient global assessment of skin, point value*	1.011	0.001			0.991	0.04		
Univariate: medical history and risk factors								
History of coronary artery disease, yes vs no*	2.111	0.04			0.555	0.16		
History of MTX, yes vs no	1.702	0.03			1.198	0.395		
History of hypertension, yes vs no	1.267	0.18			0.505	0.001		
History of diabetes, yes vs no	0.904	0.75			0.496	0.03		

Variables presented in this table were either statistically significant in at least one univariate analysis or included in a multivariate analysis. Complete univariate and multivariate analysis tables (including 95% CIs for HRs) by analysis are presented in the online supplementary appendices tables S1 and S2. In the TNFi persistence analysis, an HR >1 indicates increased risk of therapy switch and, therefore, shorter TNFi persistence. In the time to remission analysis, an HR >1 indicates increased risk of achieving remission and, therefore, achieving remission faster. In the time to loss of remission after therapy switch analysis, an HR >1 indicates increased risk of losing remission and, therefore, shorter time to loss of remission.

*Values not recorded for patients enrolled early in the study. Updates to the enrolment form added variables.

BMI, body mass index; CDAI, Clinical Disease Activity Index; mHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; NA, (data) not available; PsA, psoriatic arthritis; TNFi, tumour necrosis factor inhibitor.

the trough serum level of infliximab.³⁹ Finally, a recent analysis of two nationwide registries found that infliximab monotherapy was associated with shorter TNFi persistence than combination therapy with MTX.⁴⁰

We investigated whether there were predictors of longer or shorter TNFi persistence. We found that ethnicity, PsA duration (time since diagnosis), BMI, baseline disability and disease activity, history of coronary artery disease, and history of MTX treatment were significant predictors in this analysis. A longer PsA duration was associated with longer TNFi persistence. This characteristic was not a significant predictor of TNFi persistence in an analysis of SSATG²² and was not significantly different between patients with and without minimal disease activity (MDA) in a prospective, clinical cohort of 146 patients.⁴¹ Higher BMI was predictive of shorter TNFi persistence, which is consistent with a report that found obesity to be negatively correlated with achievement of

MDA.⁴² Greater severity of baseline disability and disease activity and a history of prior treatment with MTX were also predictive of shorter TNFi persistence. In NOR-DMARD, patient global assessment was significant in a univariate but not multivariate analysis of biologic survival.²¹ In DANBIO, an unadjusted analysis found that the number of tender joints and HAQ score were predictive of treatment discontinuation, but none of these were included in the final multivariate model.²³ Finally, the SSATG study found that baseline CRP but no other marker of disease activity (or disability) predicted longer TNFi drug survival.²²

We also investigated the time to achieving remission and predictors for longer/shorter time to remission. Our analysis showed that the median time to achieve remission was not significantly different between the combination therapy and monotherapy groups (21 vs 25 months). Notably, female sex, higher BMI, and

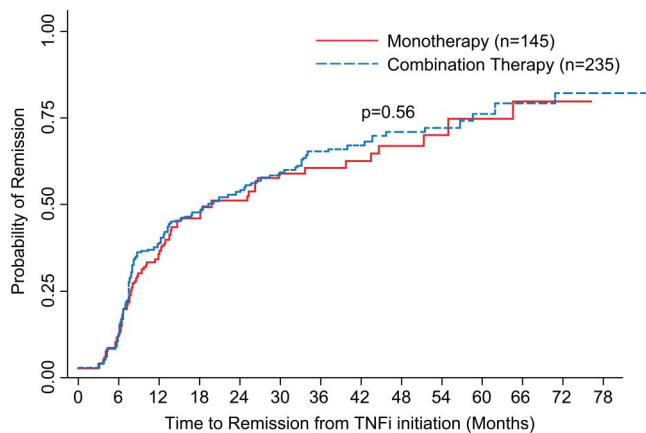


Figure 3 Time to remission. Patients were censored if remission was not achieved, a measure of remission was missing, or there was no further follow-up (TNFi, tumour necrosis factor inhibitor).

higher baseline disability and disease activity measures were significantly associated with longer time to remission. Previous analyses have found results mostly similar to ours. Female sex was negatively predictive of European League Against Rheumatism (EULAR) good response but not associated with ACR20/50/70 response in the DANBIO study.²³ In our study and in previously published analyses, obesity has been negatively associated with achieving and maintaining remission and MDA, respectively.⁴² Finally, the DANBIO study showed that a number of baseline disability and disease activity measures (HAQ, tender joint counts, swollen joint counts and low levels of CRP) were predictive of poorer clinical response (achievement of ACR improvement criteria or EULAR good response).²³

Several limitations to our study need to be mentioned. Observational studies are subject to channelling bias, that is, patients will be directed to therapies based on factors, such as TNFi persistence and remission, that may substantially affect follow-up results. Non-random factors may have led to the choice of biologic as well as the choice of combination therapy or monotherapy. We attempted to control for channelling bias between combination therapy and monotherapy by matching patients using propensity scores. Although propensity score matching reduces the effect of baseline characteristics, the resulting analysis is still not randomised and may be influenced by unmeasured or unanalysed factors. Propensity scoring also reduces the statistical power of an analysis, as shown in a Corrona study comparing csDMARDs and biologics.²⁹ Also, we used the inverse probability treatment weighting method to create weights based on the propensity score. Since we did not use propensity score matching to create two comparable monotherapy and combination therapy groups, we cannot provide a comparison of matched monotherapy vs combination therapy cohorts in order to evaluate how well other covariates are balanced. The inverse probability treatment weighting method allowed us, however, to

keep a maximal sample size, which would not have been possible with propensity score matching. Similar to propensity score matching, moreover, the inverse probability treatment weight method removed systematic differences between the monotherapy and combination therapy groups.

We were not able to assess MDA owing to the lack of two of seven required elements (body surface area and enthesitis score)⁴³ in the Corrona records we queried. Therefore, our analysis of remission did not include all the relevant disease characteristics of PsA. Another possible limitation of the remission analyses is that the CDAI has been identified as a conservative estimate of disease activity, particularly in its remission criteria.⁴⁴ Moreover, neither CDAI nor remission has been validated as disease activity measures in PsA but both are considered reasonable surrogates. Another limitation is that we did not assess reasons for TNFi discontinuation and excluded patients with less than 1 year of follow-up, possibly biasing our study population towards longer TNFi persistence. Finally, our analysis of TNFi persistence by individual TNFi may have been underpowered to avoid a type 2 error. While the results of our analysis are interesting and seem to confirm those of NOR-DMARD,²¹ prospective studies are needed to assess the comparative effectiveness of monotherapy and combination therapy in PsA.

There is variable evidence regarding the efficacy of combination therapy versus monotherapy in PsA.^{18–20} Our analysis of the Corrona registry provides insight from a US-based clinical practice perspective. Even when adjusting for channelling bias with propensity scores, TNFi persistence and time to remission were not significantly different between the combination therapy and monotherapy groups. TNFi persistence was significantly lower with infliximab monotherapy compared with combination therapy, favoured monotherapy with etanercept, and was not significantly different between therapies with adalimumab. The difference between infliximab combination therapy and monotherapy may be related to background disease severity, immunogenicity or other factors. Greater degree of disability and disease activity use were associated with shorter duration of initial therapy. Prospective, randomised clinical trials evaluating the efficacy of combination therapy versus monotherapy would provide much-needed clarity on treatment options for patients with PsA.

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