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TNFi Cycling Versus Changing Mechanism of Action in TNFi-Experienced Patients: Result of the Corrona CERTAIN Comparative Effectiveness Study

Jeffrey R. Curtis,[1] Joel M. Kremer,[2] George Reed,[3] Ani K. John,[4] and Dimitrios A. Pappas[5]

Objective. Comparative effectiveness research can inform treatment decisions regarding the choice of biologics for rheumatoid arthritis (RA). The objective of this study is to compare the efficacy of tumor necrosis factor inhibitors (TNFis) and non-TNFis (nTNFis) in real-world patients with RA and past TNFi experience.

Methods. Comparative Effectiveness Registry to study Therapies for Arthritis and Inflammatory Conditions (CERTAIN) was nested within the United States Corrona registry. Adult patients with RA with moderate to high disease activity (Clinical Disease Activity Index [CDAI] >10) with exposure to one or more prior TNFis who were switching to a new TNFi or nTNFi (choice of therapy per physician choice) were enrolled. The primary outcome was the achievement of low disease activity (LDA) at 12 months (CDAI ≤10; disease activity score in 28 joints based on C-reactive protein [DAS28-CRP] <2.67). Propensity score modeling probability of treatment with nTNFi versus TNFi adjusted for imbalanced factors. The response rate was modeled using mixed-effect logistic regression models, adjusting for a priori and imbalanced baseline factors and accounting for the practice-related treatment patterns.

Results. After applying inclusion criteria, 939 biologic initiations were analyzed, 505 (53.7%) nTNFis and 434 (46.3%) TNFis. Patients who started nTNFis were significantly more likely to have longer disease duration, more prior TNFi use, and higher patient fatigue scores and were more likely to have government insurance. At 12 months, 28% of nTNFi and 24% of TNFi initiators were in LDA by CDAI, and 22% of nTNFi and 19% of TNFi initiators were in LDA by DAS28-CRP. After multivariable adjustment and controlling for the influence of site-related confounding, there were no significant differences in the likelihood to reach LDA by CDAI (adjusted odds ratio [aOR] = 1.12; 95% confidence interval [CI], 0.78-1.62) or DAS28-CRP (aOR = 1.16; 95% CI, 0.77-1.75).

Conclusion. In this large, real-world study enrolling patients with RA with prior TNFi exposure, switching to an nTNFi biologic was comparable in its clinical effectiveness with switching to another TNFi.

INTRODUCTION

Clinicians have a variety of biologic treatment options to select from to effectively manage rheumatoid arthritis (RA). For patients who are methotrexate (MTX) or biologic naive, response rates to all the biologics are relatively comparable based largely on indirect comparisons (1–3). However, for individuals who have previously received one or multiple tumor necrosis factor inhibitors (TNFis), the decision about whether to switch ("cycle") to another TNFi medication or change biologics to one with a different mechanism of action (MOA) remains controversial.

The 2015 American College of Rheumatology (ACR) RA recommendations suggested that if a patient with RA had received TNFi therapy yet remained in moderate or high disease activity, a non-TNFi (nTNFi) biologic should be considered preferentially over switching to another TNFi agent. However, the evidence

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[1]Jeffrey R. Curtis, MD, MS, MPH: University of Alabama at Birmingham, Birmingham, Alabama; [2]Joel M. Kremer, MD: Albany Medical Center, The Corrona Research Foundation, Albany, New York; [3]George Reed, PhD: University of Massachusetts, Worcester; [4]Ani K. John, PhD, MPH, BSN: Genentech, San Francisco, California; [5]Dimitrios A. Pappas, MD, MPH: Columbia University, New York, New York.

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Address correspondence to Jeffrey R. Curtis, MD, MPH, University of Alabama at Birmingham, FOT 802; 510 20th Street South, Birmingham, AL 35294. Email: jrcurtis@uabmc.edu.

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SIGNIFICANCE & INNOVATIONS

- The evidence base on whether to choose a second or subsequent biologic after the failure of a first tumor necrosis factor inhibitor (TNFi) for patients with rheumatoid arthritis (RA) is limited. In this large prospective, protocol-driven United States registry-based study, patients who initiated a non-TNFi (nTNFi) biologic were compared with those initiating another TNFi.
- At 1 year, patients with RA initiating a new nTNFi biologic were numerically more likely to achieve low disease activity or remission, but the magnitude of difference was generally small. The largest benefit was observed among patients who had failed two or more TNFi therapies.

supporting this conditional (ie, weak) recommendation was graded as "low or very low." It was mostly informed by a few European studies that suggested that switching to rituximab had a more favorable clinical response compared with switching to another TNFi (4). Overall, although the differences in the disease activity score in 28 joints (DAS28) based on erythrocyte sedimentation rate (ESR) at 6 months favored rituximab, the magnitude was relatively small (a difference of 0.4 DAS28 units) and confined to people who discontinued the initial TNFi therapy for lack of efficacy. There was no difference observed between rituximab and TNFi in those who switched for intolerance/safety reasons. More recently, a French study randomized patients to receive a second TNFi versus a biologic with an nTNFi MOA (48% tocilizumab, 28% rituximab, and 23% abatacept). The nTNFi therapy arm was significantly better, albeit with a modest effect size (also 0.4 DAS28 units) (5).

Given this relatively limited evidence base, the generalizability concerns of the above studies, which typically enrolled patients starting in high disease activity (the mean DAS28-ESR was approximately 5.1 in both studies), and the potential influence of certain therapies (eg, tocilizumab) to preferentially improve acute phase reactants, we conducted a prospective, real-world, observational comparative effectiveness study of patients with RA and prior TNFi exposure initiating a new biologic. We tested the hypothesis that changing MOA to an nTNFi medication would result in a higher proportion of patients attaining low disease activity (LDA) using the Clinical Disease Activity Index (CDAI) and the DAS28 based on C-reactive protein (CRP). The CDAI is the most-used RA disease activity metric in the United States that incorporates physician data and is not dependent on laboratory testing, making it highly feasible for routine use in busy clinical settings.

METHODS

Overview. The Comparative Effectiveness Registry to study Therapies for Arthritis and Inflammatory Conditions (CERTAIN) study was a prospective, protocolized 12-month observational cohort study of adult patients with RA fulfilling the 1987 ACR criteria and was conducted as an ancillary study and nested within the Corrona physician network (6). Participants had to have at least moderate disease activity, defined by a CDAI score of more than 10, who were starting or switching biologic agents. To be eligible for this analysis, CERTAIN patients must have been exposed to at least one TNFi therapy previously and must have discontinued it for any reason (biologic-naive patients were enrolled into another arm of CERTAIN and reported elsewhere). Laboratory tests (eg, CRP) are required at each visit, and visits are spaced regularly at 3-month intervals. All laboratory testing was performed by a central laboratory (ICON Labs) and included a complete blood count, a metabolic panel, CRP, rheumatoid factor (RF), anti-citrullinated protein antibodies, and quantitative immunoglobulins. The primary hypothesis tested in CERTAIN is that non–anti-TNF biologics would have greater effectiveness compared with TNFi therapy to help patients reach LDA as measured by the CDAI and the DAS28-CRP at 12 months. Patients provided informed consent to participate (above and beyond their consent to participate in the parent Corrona RA registry), and the study was governed by the New England Institutional Review Boards (IRBs) (120160610) and local IRBs. Design characteristics of the CERTAIN study have been previously published (7).

Study design. CERTAIN was launched at 43 United States sites involving more than 100 clinicians and was designed to investigate the comparative effectiveness of the approved biologics for RA. The decision to start a particular biologic and offer patient enrollment in CERTAIN was at the discretion of the treating physician; patients were not randomized. Inclusion criteria for this preplanned analysis required prior exposure to one or more TNFi therapies, moderate or high disease activity (ie, CDAI >10) at baseline, initiation of a RA biologic that the patient had never previously received, and no prior exposure to any nTNFi biologic.

CERTAIN collected demographic, clinical, and laboratory data at baseline and at 3-month intervals, through 12 months, for a total of five visits according to a prespecified protocol. Patients were considered to have completed the study at the conclusion of their 12-month follow-up visit or if they switched or discontinued the biologic before 12 months. In the circumstance in which a patient discontinued a biologic and elected to initiate another, participants were offered the opportunity to re-enroll in CERTAIN with a new baseline as long as they requalified and met inclusion criteria (ie, CDAI >10) at the time of the switch. Medications were grouped as TNFi therapy (etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab) or nTNFi therapy (abatacept, rituximab, and tocilizumab). In light of the possibility that some sites might have strongly preferential use of TNFi or nTNFi therapies that could skew the overall sample to over-represent one MOA, CERTAIN enforced that the overall study recruitment of TNFi:nTNFi therapy patients be within a 2:3 or 3:2 ratio. In other words, no less than 40% and no more than 60% were permitted

to enroll in each of the two arms across the entire study, although this ratio was not enforced at each site. If enrollment was imbalanced outside of this ratio, enrollment in CERTAIN would be temporarily paused for that arm. Enrollment began in November 2010 and concluded in April 2014. For patients who dropped out of the study (eg, because they withdrew consent, moved out of the area, etc) but remained on the medication initiated at baseline at their last CERTAIN visit, they were excluded from the main analysis but were included as part of a sensitivity analysis. At most, they could miss at least one protocol-specified visit.

Outcomes. The two co-primary outcomes were LDA at 12 months, defined by CDAI of 10 or less, and DAS28-CRP of less than 2.67 (8). CRP was measured at the central laboratory using a high-sensitivity assay. For patients who remained on therapy at 12 months, their clinical outcomes were assessed at the 12-month visit. Distinct from those patients who dropped out of the study described above, for patients discontinuing the treatment before 12 months, the participant was considered to have completed the study as an early terminator, and nonresponder imputation was used for outcome classification.

Statistical analysis. Based on the prespecified analysis plan, the data were analyzed per protocol, and patients who dropped out of the study early (but remained on the therapy of interest at their last visit) were censored; the data were reanalyzed as intent to treat (ITT) as part of a sensitivity analysis. Nonresponder imputation was used for patients who terminated the study early because they discontinued the biologic treatment. The unit of analysis was treatment initiations. Given the nonrandomized nature of the study, propensity scores (PSs) were used to balance baseline patient characteristics at the time of treatment initiation, modeling the likelihood that patients received a TNFi versus an nTNFi biologic. Some covariates were forced into the PS based on subject matter expertise and decided on a priori according to a prespecified analysis plan. Forced covariates included baseline CDAI, number of prior TNFi medications, glucocorticoid use, and concomitant MTX. We also included any baseline factors that were imbalanced if the magnitude of the absolute standardized mean differences (SMDs) was greater than 0.10, following prior conventions (9). Because the characteristics of individuals initiating TNFi and nTNFi therapies were expected to be dissimilar in some respects, we excluded individuals in the nonoverlapping tails of the PS distribution in order to study only comparable patients who might have received either type of RA biologic and thus were in the region of "common support" of the PS. This a priori exclusion thus identified those participants with absolute indications or contra-indications for treatment.

A multivariable-adjusted mixed-effects logistic regression analysis was carried out to model LDA by CDAI and LDA by DAS28-CRP in separate models. Adjustment was performed to reduce residual confounding for covariates that were still not in balance (|SMD| > 0.10) after trimming outside the region of common PS support. These included age, duration of RA, insurance type, number of prior biologic disease-modifying antirheumatic drugs (DMARDs), patient global assessment, and patient fatigue. Given the potential influence that distinct factors (eg, infusion capabilities, patient management practices) present at study sites might exert on the results, study site was adjusted for as a random effect. The proportion of patients achieving LDA was plotted by study site, grouped according to whether they were higher users of TNFi therapies or nTNFi therapy, and an intraclass correlation coefficient (ICC) was computed to describes the extent to what outcomes within each cluster (ie, practice site) are likely to be similar. The factors above were then included in the multivariable logistic regression model, resulting in an adjusted estimated effect (adjusted odds ratio [aOR]) and 95% confidence interval (CI), using STATA version 15.1 procedure meqrlogit. Study recruitment was targeted to achieve at least 80% statistical power to detect a more than 10% difference between the two treatment arms. Imputation was performed for factors with less than 5% missing data (RF, anti-CCP antibody, and fatigue visual analog scale). For missing data, simple single imputation was based on factors known to be strongly correlated with the missing data (eg, patient fatigue imputed on the basis of patient pain and physician global).

Sensitivity and subgroup analyses. A variety of subgroup analyses were conducted on the basis of important characteristics. These included participants with exposure to exactly one prior TNFi versus two or more prior TNFi therapies, those who received biologic monotherapy (ie, not receiving methotrexate or any other conventional synthetic DMARD [csDMARD]), those with CRP of more than 3mg/L, and comparisons between the group of TNFis and each specific nTNFi medication (abatacept, rituximab, and tocilizumab). Additionally, because multivariable adjustment might not control as highly for baseline imbalances as matching, we performed a subgroup analysis of 1:1 PS-matched patients as an additional sensitivity analysis. One-to-one "greedy" matching with a caliper distance of 0.1 units on the logit scale was used in the matching procedure. Additional sensitivity analyses were conducted that excluded practice sites with greater imbalance in their use of TNFi or nTNFi biologics (ie, >70% or <20%; or >60% or <40% TNFi use relative to nTNFi biologics).

RESULTS

The disposition of participants in the study is shown in Figure 1. Among a total of 998 unique TNF-experienced patients with RA, a total of 1091 initiations occurred in patients who were naive to all nTNFi biologics. These individuals started TNFi (n = 515 initiations, 47.2%) and nTNFi (n = 576 initiations, 52.8%) biologics and were captured in CERTAIN (2010 to 2014). Most participants (n = 913, 91.4%) enrolled only once, although 78 (7.1% of initiations) enrolled twice, and seven people enrolled three (n = 6) or

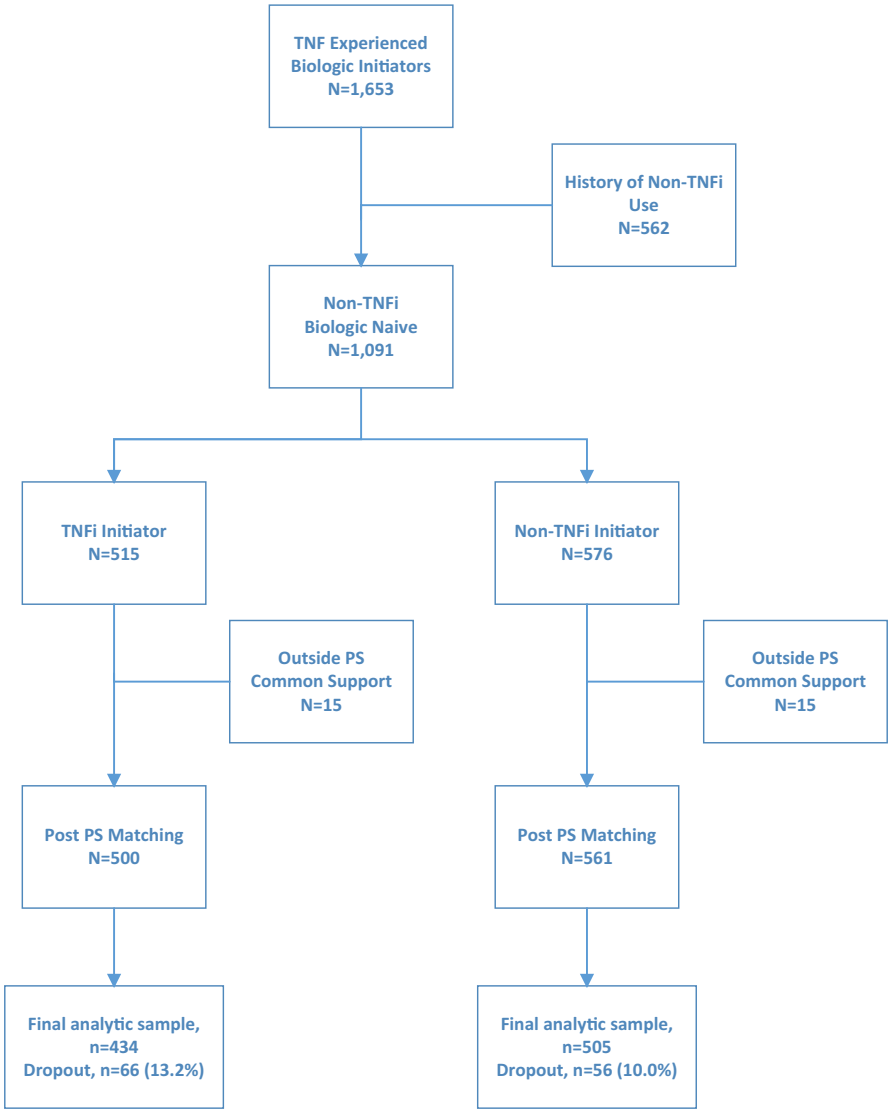

Figure 1. Selection of patients to receive tumor necrosis factor inhibitor (TNFi) or non-TNFi biologics. ET, early termination; PS, propensity score.

four (n = 1) times. A total of 30 (2.7%) had PSs outside the area of common support (Appendix Figure 1) and were excluded, leaving an effective sample size of 1061 initiations. After excluding the 11.5% of patients who dropped out of the study early (10% in the nTNFi arm and 13.2% in the TNFi arm), the sample size for the primary analysis was 939. Of these, 53.8% (505/939) were in the nTNFi arm and 46.2% (434/939) in the TNFi arm.

The most common TNFi used was infliximab (24%), followed by adalimumab and certolizumab (each 22%), etanercept (21%), and golimumab (12%). The most common nTNFi was abatacept (62%), followed by tocilizumab (29%) and rituximab (12%).

Characteristics of the 505 nTNFi and 434 TNFi initiators are shown in Table 1. As shown and based on an SMD of more than 0.10, nTNFi-treated patients were slightly older (56.9 vs 55.4 years) and had a longer duration of RA (10.0 years vs 8.7 years). The nTNFi-treated patients were more likely to have Medicare coverage (33.3% vs 25.6%), were more likely to have had a hospitalized infection (9.1% vs 6.2%), and had a greater number of prior csDMARDs (1.9 vs 1.7). They were somewhat less likely to be RF positive (64.5% vs 69.4%) and had somewhat higher fatigue scores (57.4 vs 53.4 on a 0-100 visual analog scale).

The primary study outcomes of LDA by CDAI and DAS28-CRP for the eligible analytic population (ie, in the region of common PS support) are presented in Table 2 and Figure 2. As shown, numeric trends slightly favored nTNFi medications for both the CDAI and DAS28-CRP LDA outcomes, but none were significant after adjustment. In the nTNFi group, 28% of patients attained LDA by CDAI compared with 24% of patients in the TNFi group. LDA by DAS28-CRP followed a similar pattern, with 22% in the nTNFi arm and 19% in the TNFi arm achieving LDA. Adjusting for forced covariates and residual imbalances in baseline characteristics (SMD > 0.10) yielded effect estimates that were close

Table 1. Baseline characteristics of patients with RA receiving TNFi or non-TNFi biologics

Characteristics	Non-TNFi (n = 505)	TNFi (n = 434)	SMD	*P* value*
Female sex, n (%)	404 (80.0)	350 (80.7)	0.02	0.80
Age, mean ± SD, yr	56.9 ± 12.9	55.4 ± 13.1	−0.11	0.08
Race, n (%)				
Asian	7 (1.4)	3 (0.7)	−0.07	0.30
Black	33 (6.5)	34 (7.8)	0.05	0.44
Mixed	12 (2.4)	9 (2.1)	−0.02	0.76
White	427 (84.6)	354 (81.6)	−0.08	0.22
Other	0 (0.0)	5 (1.2)	0.15	0.02
Unknown	3 (0.6)	1 (0.2)	−0.06	0.39
Hispanic	26 (5.2)	32 (7.5)	0.09	0.16
College education, n (%)	308 (61.4)	268 (62.0)	0.01	0.83
Insurance, n (%)				
No insurance	9 (1.8)	10 (2.3)	0.04	0.57
Private insurance	364 (72.1)	329 (75.8)	0.09	0.20
Medicaid	43 (8.5)	31 (7.1)	−0.05	0.44
Medicare	168 (33.3)	111 (25.6)	−0.17	0.01
BMI, mean ± SD	30.1 ± 7.2	30.5 ± 7.1	0.07	0.32
Normal (<25), n (%)	130 (25.7)	94 (21.7)	−0.10	0.14
Overweight (25.0-29.9), n (%)	161 (31.9)	142 (32.7)	0.02	0.78
Obese (30.0-34.9), n (%)	108 (21.4)	90 (20.7)	−0.02	0.81
Very obese (≥35), n (%)	104 (20.6)	105 (24.2)	0.09	0.19
Smoking status, n (%)				
Never	236 (47.0)	196 (46.1)	−0.02	0.79
Former	170 (33.9)	146 (34.4)	0.01	0.88
Current	96 (19.1)	83 (19.5)	0.01	0.88
Employment, n (%)				
Full time	173 (34.5)	163 (38.1)	0.07	0.26
Part time	50 (10.0)	34 (7.9)	−0.07	0.28
At home	39 (7.8)	36 (8.4)	0.02	0.73
Student	39(7.8)	33 (7.7)	−0.00	0.97
Disabled	94 (18.8)	76 (17.8)	−0.03	0.69
Retired	106 (21.2)	86 (20.1)	−0.03	0.69
Duration of RA, mean ± SD, yr	10.0 ± 8.9	8.7 ± 9.1	−0.14	0.03
RF positive, n (%)	320 (64.5)	297 (69.7)	0.11	0.09
CCP positive, n (%)	298 (62.2)	267 (65.3)	0.06	0.34
Systolic blood pressure, mean ± SD	126.5 ± 16.3	126.0 ± 16.2	−0.03	0.62
Diastolic blood pressure, mean ± SD	76.0 ± 10.4	76.2 ± 10.2	0.01	0.85
Comorbidities, n (%)				
Hospitalized infection	46 (9.1)	27 (6.2)	−0.11	0.10
CVD	57 (11.3)	40 (9.2)	−0.07	0.30
Malignancy	33 (6.5)	24 (5.5)	−0.04	0.52
RA therapies, n (%)				
Exactly one prior TNFi	243 (48.1)	323 (74.4)	0.56	0.00
Exactly two prior TNFis	193 (38.2)	96 (22.1)	−0.36	0.00
Three or more prior TNFis	69 (13.7)	15 (3.5)	−0.37	0.00
Monotherapy	161 (31.9)	136 (31.3)	−0.01	0.86
Combination therapy	344 (68.1)	298 (68.7)	0.01	0.86
Prednisone use (any)	183 (36.2)	154 (35.5)	−0.02	0.81
Prednisone ≤10 mg/d	160 (31.7)	141 (32.5)	0.02	0.79
Prednisone >10 mg/d	23 (4.6)	13 (3.0)	−0.08	0.22
Assessments				
TJC, mean ± SD	11.1 ± 7.5	11.3 ± 7.8	0.03	0.61
SJC, mean ± SD	7.4 ± 5.2	7.6 ± 5.7	0.04	0.58
Physician global (range, 0-100), mean ± SD	49.3 ± 18.8	50.2 ± 19.5	0.05	0.45
Patient global (range, 0-100), mean ± SD	54.4 ± 24.4	52.1 ± 24.8	−0.10	0.14
CDAI, mean ± SD	28.8 ± 12.6	29.1 ± 13.8	0.02	0.72
Moderate (>10-22), n (%)	168 (33.3)	164 (37.8)	0.09	0.15
High (>22), n (%)	337 (66.7)	270 (62.2)	−0.09	0.18
DAS28-CRP, mean ± SD	4.76 ± 1.1	4.7 ± 1.1	−0.02	0.77
Low, n (%)	10 (2.06)	13 (3.08)	0.07	0.33
Moderate, n (%)	125 (25.72)	118 (27.96)	0.05	0.45

(Continued)

Table 1. *(Cont'd)*

Characteristics	Non-TNFi (n = 505)	TNFi (n = 434)	SMD	*P* value*
High, n (%)	351 (72.22)	291 (68.96)	−0.07	0.28
Patient pain (0-100), mean ± SD	55.4 ± 25.6	53.5 ± 26.3	−0.07	10.26
Fatigue (0-100), mean ± SD	57.4 ± 28.6	53.4 ± 28.6	−0.14	0.03
Morning stiffness, n (%)	455 (91.7)	384 (90.0)	−0.06	0.34
None	41 (8.3)	43 (10.1)	0.06	0.33
1-29 min	69 (13.9)	53 (12.5)	−0.04	0.52
30-59 min	80 (16.2)	65 (15.3)	−0.02	0.73
60-119 min	128 (25.9)	110 (25.9)	0.00	0.98
≥120 min	177 (35.8)	153 (36.1)	0.01	0.92
CRP, mg/L	8.9 ± 13.7	9.5 ± 17.6	0.04	0.55

Abbreviations: BMI, body mass index; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28, disease activity score in 28 joints; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; SMD, standardized mean difference; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor.
N = 939.

to significant (aOR = 1.37 [95% CI, 0.98-1.91] for the CDAI outcome; aOR = 1.41 [95% CI, 0.97-2.10] for the DAS28CRP outcome). However, these effect estimates were attenuated toward the null after controlling for site clustering. The aOR for achieving LDA by CDAI was 1.12 (95% CI, 0.78-1.62) and was 1.16 (95% CI, 0.77-1.75) for DAS28-CRP. With additional adjustment for the clustering both by site and by within-person (because 7.1% of patients had more than one biologic initiation), the aOR for LDA by CDAI was nearly identical (aOR = 1.13 [95% CI, 0.76-1.67]). Analyzing the CDAI and DAS28-CRP as a continuous variable, the adjusted mean change (95% CI) in the CDAI was 0.1 (–1.6 to 1.8) units and was 0.10 (–0.10 to 0.29) units for the DAS28-CRP. Results from the ITT sensitivity analyses that included all participants (n = 1061), adding back the 11.5% of patients who were censored because they dropped out early from the study, were similar to those of the main analysis, as were results from the 1:1 PS-matched analysis (not shown).

Key subgroup analyses are shown in Figure 2. Results were similar for those having failed exactly one TNFi (aOR = 0.96 [95% CI, 0.61-1.52]), whereas those having failed two or more TNFis were numerically more likely to respond to nTNFi treatment (aOR = 1.81 [95% CI, 0.94-3.50]). Trends also suggested that monotherapy patients not on any background csDMARD were more likely to respond to nTNFi therapy (aOR = 1.38 [95% CI, 0.72-2.65]).

In an exploration of the underlying effect of the influence of site on multivariable adjustment, the proportion of CDAI responders attaining LDA is shown in Figure 3, stratified by whether sites enrolled a higher or lower proportion of nTNFi biologic initiators. As demonstrated, sites that were more likely to use nTNFi biologics (right-hand side of the figure) had higher overall responses in both treatment arms compared with sites that used a lower proportion of nTNFi biologics. The ICC for the clustering effect by site was 0.094. An adjusted analysis that excluded the sites where there was greater imbalance in use of TNFi or nTNFi biologics yielded similar results to the main analysis (excluding patients at sites with >70% or <20% TNFi use [n = 890], aOR = 1.11 [95% CI, 0.78-1.60]; excluding patients at sites with >60% or <40% TNFi use [n = 469], aOR = 1.00 [95% CI, 0.62-1.64]).

DISCUSSION

In this real-world analysis of patients with RA starting a new nTNFi or TNFi biologic after prior exposure to one or more TNFi therapies, we found no significant difference between either treatment option. Numeric trends somewhat favored an nTNFi,

Table 2. Crude and adjusted treatment response comparing non-TNFi with TNFi treatment

Disease Activity Measure	Achievement of LDA	Response Model	OR (95% CI)
CDAI	Non-TNFi: 28% TNFi: 24%	Unadjusted	1.23 (0.92-1.65)
		Adjusted for forced covariates and all covariates with SMD >0.1	1.37 (0.98-1.91)
		Adjusted for forced covariates and covariates with SMD >0.1, and adjusted for clustering by site	1.12 (0.78-1.62)
DAS28CRP	Non-TNFi: 22% TNFi: 19%	Unadjusted	1.21 (0.88-1.68)
		Adjusted for forced covariates and all covariates with SMD >0.1	1.41 (0.97-2.10)
		Adjusted for forced covariates and covariates with SMD >0.1, and adjusted for clustering by site	1.16 (0.77-1.75)

Abbreviations: CDAI, Clinical Disease Activity Index; CI, confidence interval; DAS28, disease activity score in 28 joints; LDA, low disease activity; OR, odds ratio; TNFi, tumor necrosis factor inhibitor.
N = 939.

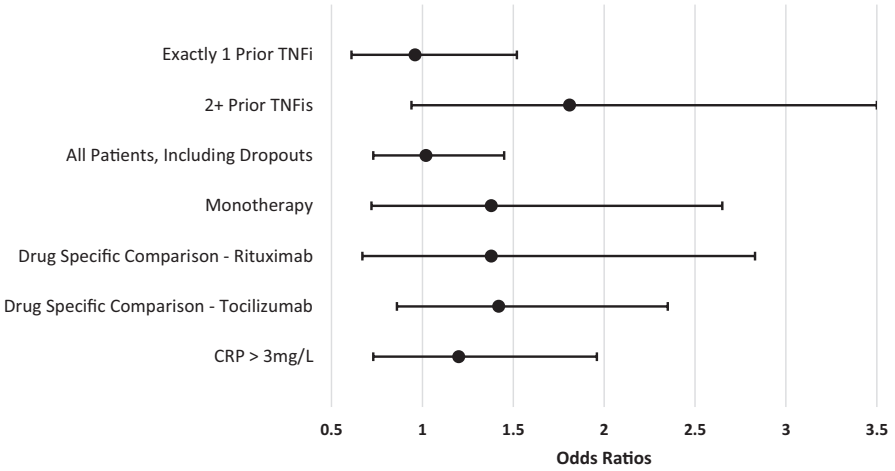

Figure 2. Subgroup analyses showing likelihood of attaining low disease activity as measured by Clinical Disease Activity Index (CDAI), comparing non–tumor necrosis factor inhibitor (TNFi) biologics to TNFi biologics (referent).CRP, C-reactive protein.

particularly in the subgroup of patients with two or more prior TNFi therapies and for those receiving biologic monotherapy, but despite the large sample size of this cohort, none were significant. Findings were robust in a variety of sensitivity analyses.

These results are perhaps at odds with prior cohort studies suggesting a benefit with nTNFi therapy over TNFi after prior exposure to a single TNFi. The French Rotate or Change (RoC) trial compared these two strategies among 300 patients with RA with the erosive disease who had exposure to exactly one prior TNFi therapy (5) and who had not discontinued their TNFi therapy because of only adverse events. It found that the nTNFi arm had a 17.2% greater likelihood to attain a European League Against Rheumatism (EULAR) good or moderate response at Week 24 (P = 0.004). At all time points (Weeks 12, 24, and 52), the mean change between groups in the DAS28-ESR was small (eg, –0.43 units at 24 weeks), and differences were always smaller than the measurement error of the DAS28-ESR (0.6 units) (10). This finding suggests that many patients may have been on the cusp of response and that many narrowly missed meeting the EULAR response criteria. Results at 24 weeks remained significant and of a similar magnitude as those at Week 52. Factors that may have accounted for the higher proportion of patients responding in the RoC study may include differences in the outcome (EULAR good/moderate response in the RoC study vs LDA by CDAI or DAS28-CRP in CERTAIN) and the proportion of patients on monotherapy (approximately 23% in RoC and 32% in CERTAIN). Additionally, the nTNFi distribution was different between the two studies. In the RoC study, the distribution of nTNFi therapies was 48% tocilizumab, 28% rituximab, and 23% abatacept), a pattern quite different than in CERTAIN, in which abatacept accounted for two-thirds of nTNFi treatment. As another potential difference between these studies, we note that only 21% to 26% of patients enrolled in CERTAIN had a normal body mass index (18.5-25). Although not a confounder between the two treatment arms in this study

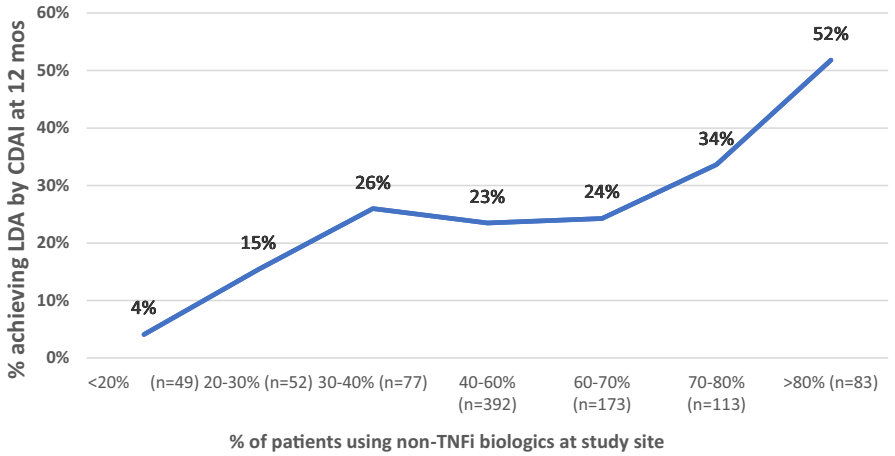

Figure 3. Low disease activity (LDA) at 12 months stratified by proportion of non–tumor necrosis factor inhibitor (TNFi) biologic initiators at each site. CDAI, Clinical Disease Activity Index.

(SMD = 0.07; P = 0.32), RA treatment response for some therapies, including TNFis, has been shown to vary in relation to obesity (16,17), which may limit the generalizability of international studies compared with the typical United States practice mix of patients with RA as was enrolled in CERTAIN. However, the direction of confounding due to obesity would be expected to yield a somewhat better treatment response in the nTNFi arm of CERTAIN, yet we did not observe a significant beneficial effect, leading us to conclude that the influence of obesity on this study's results is likely to be small.

Other studies of patients with prior exposure to TNFi therapy have suggested that nTNFi therapy may have preferential benefits, but this result may be restricted to particular subgroups. For example, prior RA studies comparing rituximab with a second TNFi suggest preferential benefit for rituximab over a subsequent TNFi (–1.5 versus –1.1; P = 0.007) (4). This and other observational studies have shown similar trends, albeit with small effect sizes (11–13) in seropositive patients, those with exposure to more than one TNFi, and in those who discontinued their previous TNFi therapy for lack of clinical efficacy (4,14,15).

Of interest, we found that site-related clustering had an important confounding effect on our results. For both LDA outcomes (CDAI and DAS28-CRP), the odds ratios for LDA were meaningfully attenuated from approximately 1.4 to 1.1 after controlling for site clustering. Further exploration revealed that patients treated at sites that used nTNFi treatments in a higher proportion of their patients with RA had a better absolute response as measured by the CDAI. Given that practice sites that preferentially prescribed non-TNFi biologic DMARDs had overall better clinical outcomes compared with sites that favored using a second TNFi, controlling for site clustering effects in the multivariable model would seem warranted. This finding and the small to moderate size ICC of 0.094 that we observed illustrate the importance for future studies to account for practice site as a potential confounding influence that should be considered in the design and/or analytic phase of a study (18,19). Although we can only speculate on the mechanism by which sites that prefer nTNFi would have better outcomes, possibilities include a variety of factors correlated with "earlier adopters," including an infrastructure more likely to engage in clinical trials, clinicians with greater familiarity with newer medications, more robust infusion capabilities (relevant because, initially, all three nTNFi biologics were only available intravenously), and payer mix limiting access to certain RA therapies that might affect patient compliance and ability to switch treatments. As we are unaware of prior observations like this, we would invite replication of this finding.

There are several limitations to CERTAIN that should be considered. First, although all patients had prior exposure to at least one TNFi therapy, the reasons for discontinuation were not systematically collected in the registry prior to 2010, and discontinuation could have occurred for a variety of reasons. The reasons for discontinuation of a prior biologic may relate to the subsequent likelihood of treatment response to a different medication. However, the published literature typically makes it difficult to quantify the number of patients excluded for this reason at the screening stage, and thus the impact of this inclusion criteria on the generalizability of a study's results is unknown. Future studies may benefit by paying attention to capturing both the duration of prior biologic therapy and the reason(s) for discontinuation, as these factors may serve as effect modifiers. Secondly, more than 60% of nTNFi-treated patients received abatacept, and thus our ability to compare to tocilizumab or rituximab was somewhat limited. Finally, CERTAIN was nonrandomized, and although PSs were used to adjust for imbalances between treatment groups, almost all imbalanced factors favored the TNFi group. Thus, any residual confounding would be biased against the nTNFi group, and our results may therefore be viewed as conservative.

In conclusion, in a large cohort of unselected patients with RA, we found some evidence to support choosing an nTNFi therapy over a subsequent TNFi, albeit with a small effect size. Our interpretation of these results is tempered by stronger numeric trends that might make exceptions for patients who have failed two or more TNFi treatments and those receiving biologics as monotherapy. The influence of practice site and the potentially confounding effects of that influence on overall patient outcomes is an interesting observation that deserves replication and consideration in the design and conduct of future real-world evidence studies.

AUTHOR CONTRIBUTIONS

Dr. George Reed had full access to the data and takes responsibility for integrity and accuracy of analysis. All authors responsible for study conception and design and for analysis and interpretation; all authors except Ani John responsible for acquisition of data.

Study conception and design. Curtis, Kremer, Reed, John, Pappas.

Acquisition of data. Curtis, Kremer, Reed, John, Pappas.

Analysis and interpretation of data. Curtis, Kremer, Reed, John, Pappas.

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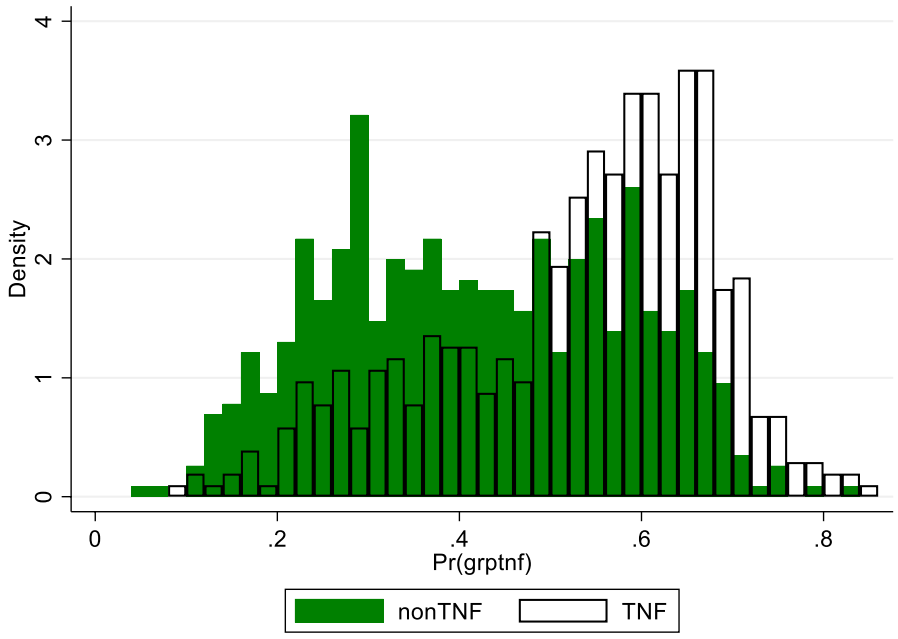
APPENDIX



Appendix Figure 1. Propensity Score Distribution in tumor necrosis factor inhibitor (TNFi) and non-TNFi patients.