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Real-World Comparative Effectiveness of Tofacitinib and Tumor Necrosis Factor Inhibitors as Monotherapy and Combination Therapy for Treatment of Rheumatoid Arthritis

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ORIGINAL RESEARCH

Real-World Comparative Effectiveness of Tofacitinib and Tumor Necrosis Factor Inhibitors as Monotherapy and Combination Therapy for Treatment of Rheumatoid Arthritis

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ABSTRACT

Introduction: No published studies exist comparing the effectiveness of tofacitinib with other advanced therapies for the treatment of rheumatoid arthritis (RA) in real-world clinical practice. Here, we report differences in effectiveness of tofacitinib compared with standard of care, tumor necrosis factor inhibitors (TNFi), with or without concomitant methotrexate (MTX), using US Corrona registry data.

Methods: This observational cohort study included RA patients receiving tofacitinib (from 6 November 2012; $N = 558$) or TNFi (from 1 November 2001; $N = 8014$) with or without MTX until 31 July 2016. Efficacy outcomes at 6 months included modified American College of Rheumatology 20% responses, Clinical Disease Activity Index (CDAI) and Pain. Outcomes were compared between patients receiving TNFi and tofacitinib with or without MTX and by line of therapy. Outcomes within therapy lines were compared using propensity-score matching; between-group differences were estimated using mixed-effects regression models.

Results: Patients receiving tofacitinib had longer RA duration and a greater proportion had previously received biologics than those receiving TNFi; other baseline characteristics were comparable. In patients receiving second- and third-line TNFi therapy, CDAI low disease activity/remission response rates were significantly better with concomitant MTX. Too few patients received tofacitinib as second line for meaningful assessment. No significant differences were observed in outcomes between tofacitinib as monotherapy and tofacitinib with concomitant MTX.

Conclusions: In clinical practice, TNFi efficacy is improved with concomitant MTX in the second and third line. In the third/fourth line, patients are likely to achieve similar efficacy

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with tofacitinib monotherapy, or TNFi or tofacitinib in combination with MTX.
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Key Summary Points

Why carry out this study?

Although tofacitinib has been evaluated in randomized controlled trials, no studies currently exist that assess its effectiveness in rheumatoid arthritis (RA) relative to existing standard of care, tumor necrosis factor inhibitor (TNFi), in real-world clinical practice.

What was learned from the study?

This is the first study to demonstrate the comparative effectiveness of tofacitinib versus TNFi for RA in real-world clinical practice.

In the US Corrona registry, tofacitinib as monotherapy or with concomitant methotrexate (MTX) provided similar efficacy in the third/fourth line.

Tofacitinib with or without MTX achieved similar efficacy to TNFi with MTX in the third/fourth line.

Concomitant MTX improved efficacy of TNFi in the second/third line.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by systemic inflammation, persistent synovitis, and joint destruction. The target of therapy for RA is to achieve remission, or low disease activity (LDA) if remission is not achievable [1, 2]. The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) recommend the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; usually methotrexate [MTX]) as first-line therapy in patients with RA [1, 2]. However, the use of MTX has been shown to achieve remission in less than one-third of patients [3]. Therefore, in patients who have an inadequate response to therapy with csDMARDs, the addition of either a biologic DMARD (bDMARD), such as a tumor necrosis factor inhibitor (TNFi), or a targeted synthetic DMARD, such as a Janus kinase (JAK) inhibitor, either as monotherapy or in combination with other csDMARDs, is recommended by both ACR and EULAR [1, 2].

Tofacitinib is an oral JAK inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) administered as monotherapy or in combination with csDMARDs, mainly MTX, in patients with moderately to severely active RA, have been demonstrated in phase 2 [4–8], phase 3 [9–14], and phase 3b/4 [15] studies of up to 24 months' duration, and in long-term extension (LTE) studies with up to 9.5 years of observation [16–18]. Tofacitinib 5 mg BID is approved in several countries for use in adults with moderately to severely active RA with an inadequate response or intolerance to MTX, and can be administered alone or in combination with csDMARDs. In a 1-year, double-blind, phase 3b/4, head-to-head, non-inferiority, randomized controlled trial (RCT) of adult patients with active RA and an inadequate response to MTX (ORAL Strategy), the efficacy of tofacitinib and MTX combination therapy was shown to be non-inferior to adalimumab and MTX combination therapy, while tofacitinib monotherapy was not shown to be non-inferior to either combination [15]. Although tofacitinib has been evaluated in RCTs, no studies currently exist that assess its effectiveness in RA relative to existing standard of care, TNFi, in real-world clinical practice. Here, we characterize the comparative effectiveness of tofacitinib and TNFi as monotherapy and in combination with MTX using data from the US Corrona RA registry, a large independent, prospective, observational database of patients with RA recruited from 174 private and academic practice sites

across 41 states in the US with 696 practicing rheumatologists [19, 20].

METHODS

Study Design and Patient Population

Patients with RA in the US Corrona registry were included in the analysis if they had initiated treatment with tofacitinib or a TNFi (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol) during the observation period (1 November 2001 to 31 July 2016). As of September 2017, the Corrona registry consists of a prospective US observational cohort of patients with arthritis who are enrolled by more than 696 participating rheumatologists representing 174 private and academic practices across 41 states. This study was carried out in accordance with the Declaration of Helsinki. All participating investigators were required to obtain full board approval for conducting noninterventional research involving human subjects with a limited dataset. Sponsor approval and continuing review was obtained through a central Institutional Review Board (IRB), the New England Independent Review Board (NEIRB; no. 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective governing IRBs and documentation of approval was submitted to Corrona, LLC prior to the initiation of any study procedures. All patients in the registry were required to provide written informed consent and authorization prior to participating. At the time of enrolment in the registry and during follow-up, patients and physicians completed a questionnaire assessing past and present disease characteristics, disease activity measurements and other standard patient-reported outcomes. To be included in the efficacy assessment, patients were required to have a 6-month follow-up visit (defined as a clinical visit within 4–9 months of enrolment; in the event of more than one visit within this timeframe, the closest to 6 months was used) and Clinical Disease Activity Index (CDAI) measured at baseline and follow-up. Tofacitinib and TNFi could be initiated as monotherapy (without concomitant use of any csDMARD) or combination therapy (with concomitant MTX but no other csDMARD). Data from patients receiving tofacitinib or TNFi therapy in combination with any csDMARD other than MTX were excluded from this analysis.

Outcomes

Efficacy outcomes included achievement of LDA or remission based on CDAI score (LDA: CDAI > 2.8–10; remission: CDAI ≤ 2.8 [21]) at 6-month follow-up. Other outcomes of interest included: the proportion of patients achieving modified ACR 20% (mACR20) responses [22] (requiring at least 20% improvement in both tender and swollen joint counts and in two of the following end points: Patient's Global Assessment of disease activity, Physician's Global Assessment of disease activity, patient-reported pain [measured by visual analogue scale; VAS] and Health Assessment Questionnaire-Disability Index score); mean changes from baseline in CDAI score; and patient-reported pain (VAS) at 6 months.

Outcomes at 6 months were used for patients who did not switch to another bDMARD or JAK inhibitor. If a patient had switched within 6 months, for binary variables (CDAI LDA/remission [≤ 10] and mACR20 responses), the patient was classified as a non-responder to therapy; for continuous outcomes (change from baseline in CDAI and pain [VAS] scores), the last observed value prior to switching was used.

Analyses

Efficacy outcomes were compared between TNFi combination therapy and TNFi monotherapy using data collected from 1 November 2001 to 31 July 2016. In comparisons involving tofacitinib, data collection was restricted to a period beginning on the approval date for tofacitinib (from 6 November 2012 to 31 July 2016). Patient data for efficacy outcomes were categorized by line of therapy, with second line defined as prior use of at least one csDMARD and no bDMARD, third line as prior use of at

least one csDMARD and one bDMARD, and fourth line as prior use of at least one csDMARD and at least two bDMARDs. Owing to small sample sizes, effectiveness evaluations could not be performed in patients receiving tofacitinib as second-line therapy; for the same reason, data from patients initiating third- and fourth-line therapy with tofacitinib were combined.

Propensity-score matching was used to compare outcomes between comparator drug groups stratified by each line of therapy [23]. Covariates used in the propensity model were selected based on a standardized difference greater than 0.1 between comparator drug groups [24]. The covariates used for matched comparisons are listed in full below the relevant tables; all covariates considered are shown in Table S1, Online Supplementary File. Mixed-effects regression models were used to estimate differences in outcomes between the drug groups with matched pairs as the random effect; [25] logistic models were used to compare binary outcomes and provided odds ratios (ORs) and 95% confidence intervals (95% CIs); linear regression models were used to compare continuous outcomes and provided mean differences (MD) and 95% CIs. A sensitivity analysis was carried out using Inverse-Probability Weighting with Regression Adjustment (IPWRA) based on the propensity score to illustrate the robustness of the results and provide *P* values [26].

RESULTS

Patients

A total of 558 patients initiating therapy with tofacitinib and 8014 patients initiating therapy with TNFi were identified in the Corrona database. Lines of therapy are shown in Table S2, Online Supplementary File. Of these, the efficacy population (i.e., patients for whom 6 months of follow-up data were available) included 402 patients receiving tofacitinib (monotherapy, $n = 238$; combination therapy with MTX, $n = 164$) and 6241 patients receiving TNFi (monotherapy, $n = 1889$; combination therapy with MTX, $n = 4352$).

Among patients who initiated therapy with tofacitinib, 46.9% (23/49), 57.0% (45/79) and 62.7% (267/426) of patients in the second, third, and fourth line, respectively, received monotherapy (Table S2, Online Supplementary File). Among patients who initiated therapy with TNFi, 20.9% (745/3557), 35.7% (888/2490), and 41.7% (700/1678) of patients in the second, third, and fourth line, respectively, received monotherapy. A comparison of baseline demographics and disease characteristics for patients with a 6-month follow-up visit (included in the analysis) versus those without a 6-month visit showed no significant differences for patients initiating therapy with tofacitinib; patients with 6-month visits were slightly older (59.5 vs. 57.4 years; $p = 0.08$) and had similar baseline CDAI scores (20.6 vs. 20.9; $p = 0.9$) compared with patients without 6-month visits. For patients initiating therapy with TNFi, duration of RA was significantly shorter (8.8 vs. 10.0 years; $p < 0.001$) for patients with a 6-month visit compared to those without a 6-month visit, and other characteristics were similar (e.g., baseline CDAI score 21.0 vs. 21.1; $p = 0.8$).

In patients included in the analysis, the duration of RA was longer, and the proportion of bDMARD-naïve patients was lower among patients receiving tofacitinib compared with patients receiving TNFi; however, disease severity was similar between groups (Table 1; patient demographics by line of therapy [Tables S3–S5] and for matched comparisons [Table S6] are provided in the online supplementary file).

Baseline characteristics were broadly comparable between patients who initiated tofacitinib monotherapy and those who initiated tofacitinib in combination with MTX, although patients receiving combination therapy appeared to have had a slightly longer duration of RA at baseline. Among patients receiving TNFi, patients who received monotherapy had a slightly lower median age, were less likely to be bDMARD-naïve, reported higher pain and had slightly longer median duration of RA than patients who received TNFi

Table 1 Baseline demographics and characteristics for patients receiving tofacitinib and TNFi with or without concomitant methotrexate

	Tofacitinib (6 November 2012–31 July 2016)			TNFi (1 November 2001–31 July 2016)		
	Comb. (*N* = 164)	Mono. (*N* = 238)	*P* value	Comb. (*N* = 4352)	Mono. (*N* = 1889)	*P* value
Median age, years (IQR)	61 (53–68)	59 (52–68)	0.600	56 (48–65)	55 (46–64)	< 0.001
Female, *n* (%)	137 (83.5)	193 (81.1)	0.531	3353 (77.0)	1495 (79.1)	0.068
Race, white, *n* (%)	130 (79.3)	197 (82.8)	0.376	3620 (83.2)	1594 (84.4)	0.239
Median duration of RA, years (IQR)	12 (5–21)	10 (5–16)	0.058	5 (2–12)	6 (2–14)	< 0.001
Median CDAI, (IQR)	20.3 (9.5–31.0)	17.9 (9.8–27.0)	0.163	18.5 (10.0–29.1)	19.0 (10.0–29.5)	0.580
CDAI, *n* (%)						
Remission (≤ 2.8)	10 (6.1)	19 (8.0)	0.473	290 (6.7)	142 (7.5)	0.222
LDA (> 2.8–10)	33 (20.1)	43 (18.1)	0.606	813 (18.7)	342 (18.1)	0.590
Moderate (> 10–22)	46 (28.0)	83 (34.9)	0.150	1507 (34.6)	630 (33.4)	0.329
Severe (> 22)	75 (45.7)	93 (39.1)	0.184	1742 (40.0)	775 (41.0)	0.460
Median HAQ-DI (IQR)	1.3 (0.8–1.8)	1.1 (0.5–1.7)	0.148	0.9 (0.4–1.5)	1.0 (0.4–1.4)	0.382
Median patient-reported pain (VAS; IQR)	55.5 (30–75)	52.5 (25–75)	0.873	45 (20–70)	50 (25–75)	< 0.001
Prednisone use, *n* (%)	52 (31.7)	65 (27.3)	0.341	1268 (29.1)	562 (29.8)	0.624
Prednisone dose in mg, mean (SD)	4.3 (1.1)	4.4 (1.0)	0.607	4.1 (1.2)	4.4 (1.1)	< 0.001
bDMARD-naïve, *n* (%)	21 (12.8)	23 (9.7)	0.322	2345 (53.9)	685 (36.3)	< 0.001

These data represent all patients initiating treatment with TNFi or tofacitinib with 6-month follow-up data available
HAQ-DI data were not collected until June 2010
Demographic details restricted to patients included in the matched analyses are presented in Table S6, Online Supplementary File
CDAI Clinical Disease Activity Index, *Comb*. combination therapy with methotrexate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *IQR* interquartile range, *LDA* low disease activity, *Mono*. monotherapy, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor, *VAS* visual analogue scale

in combination with MTX. When TNFi data were restricted to an observation period beginning on the approval date of tofacitinib including only third-/fourth-line patients, baseline characteristics were generally comparable across groups. Figure S1 in the online supplementary file illustrates the propensity-score distributions estimated for the matched analysis.

Outcomes

TNFi Combination Therapy Versus TNFi Monotherapy

In the matched analysis of patients initiating second-line therapy with TNFi, the rate of LDA/remission (CDAI ≤ 10) was significantly higher among patients receiving TNFi with combination therapy than among those receiving TNFi

monotherapy (59.0 vs. 49.0%, respectively; OR [95% CI]: 1.50 [1.19 to 1.88]; Table 2 and Fig. 1). This analysis also showed significantly higher mACR20 response rates among patients receiving TNFi combination therapy than among those receiving TNFi monotherapy (35.9 vs. 27.8%, respectively; OR [95% CI]: 1.49 [1.15 to 1.93]; Table 2 and Fig. 1). Mean pain (VAS) at 6 months was significantly lower for patients receiving TNFi combination therapy than those receiving TNFi monotherapy. Mean decreases from baseline (i.e., improvement) in CDAI scores appeared to be greater for patients receiving TNFi combination therapy than those receiving TNFi monotherapy, but were not statistically significant. IPWRA analysis results reflected the main findings for CDAI LDA/remission and mACR20 (Table S7, Online Supplementary File).

Among patients who initiated third-line therapy with TNFi, rates of LDA/remission (CDAI $\leq$ 10) were significantly better in patients receiving TNFi combination therapy than those receiving TNFi monotherapy (43.1 vs. 36.9%; OR [95% CI]: 1.30 [1.02 to 1.64]); mACR20 response rates were not significantly different between TNFi in combination with MTX and TNFi monotherapy (24.3 vs. 21.0%; OR [95% CI]: 1.22 [0.92 to 1.63]) (Table 2 and Fig. 1). Among patients who initiated fourth-line therapy with TNFi, no differences could be discerned between patients receiving TNFi combination therapy and patients receiving TNFi monotherapy in rates of LDA/remission (32.0 vs. 34.0%; OR [95% CI]: 0.91 [0.68 to 1.23]) or for those achieving mACR20 (24.2 vs. 20.2%; OR [95% CI]: 1.27 [0.90 to 1.78]) (Table 2 and Fig. 1). IPWRA analysis results reflected the main findings (Table S8, Online Supplementary File). Unadjusted values for these efficacy outcomes in all patients initiating TNFi are provided in Table S9, Online Supplementary File.

Tofacitinib Combination Therapy Versus Tofacitinib Monotherapy

In patients who initiated third- and fourth-line therapy with tofacitinib, LDA/remission rates (32.1 vs. 30.2%; OR [95% CI]: 1.09 [0.61 to 1.95]) and mACR20 response rates (17.9 vs. 19.4%; OR [95% CI]: 0.87 [0.39 to 1.93]) were not significantly different between patients receiving tofacitinib combination therapy and patients receiving tofacitinib monotherapy (Table 3 and Fig. 2). Mean CDAI change from baseline (− 3.4 vs. − 2.6; MD [95% CI]: − 0.82 [− 4.47 to 2.82]) and mean pain (VAS) (48.3 vs. 49.1; MD [95% CI]: − 0.84 [− 8.75 to 7.07]) were also comparable between patients receiving tofacitinib combination therapy and monotherapy, respectively. IPWRA analysis results reflected the main findings (Table S7, Online Supplementary File). Unadjusted values for these efficacy outcomes in all patients initiating tofacitinib are provided in Table S9, Online Supplementary File.

TNFi Combination Therapy Versus Tofacitinib Monotherapy

When the TNFi data were restricted to an observation period beginning on the approval date of tofacitinib and matched by line of therapy (combined third and fourth line), the rates of LDA/remission (CDAI $\leq$ 10) among patients receiving TNFi combination therapy were comparable with those of patients receiving tofacitinib monotherapy (33.8 vs. 29.9%; OR [95% CI]: 1.21 [0.74 to 1.97]) (Table 4 and Fig. 2). There were also no significant differences between patients receiving TNFi combination therapy and those receiving tofacitinib monotherapy in mean change from baseline in CDAI (− 3.3 vs. − 3.9; MD [95% CI]: 0.58 [− 2.55 to 3.71]), mean pain (VAS) (49.0 vs. 48.5; MD [95% CI]: 0.44 [− 5.75 to 6.64]) or response rates for mACR20 (18.4 vs. 20.7%; OR [95% CI]: 0.87 [0.49 to 1.53]), respectively (Table 4 and Fig. 2). IPWRA analysis results reflected the main findings (Table S7, Online Supplementary File).

TNFi Combination Therapy Versus Tofacitinib Combination Therapy

When TNFi data were restricted to an observation period beginning on the approval date of tofacitinib and matched by line of therapy (combined third and fourth line), there were no differences between patients initiating treatment with TNFi combination therapy and those

Table 2 Matched analysis of outcomes for patients initiating TNFi monotherapy versus combination therapy

	Second line			Third line			Fourth line		
	Comb. (*N* = 600)	Mono. (*N* = 600)	Comparison	Comb. (*N* = 590)	Mono. (*N* = 590)	Comparison	Comb. (*N* = 400)	Mono. (*N* = 400)	Comparison
CDAI LDA/ remission,[a] *n* (%)	354 (59.0)	294 (49.0)	OR (95% CI): 1.50 (1.19 to 1.88)	254 (43.1)	218 (36.9)	OR (95% CI): 1.30 (1.02 to 1.64)	128 (32.0)	136 (34.0)	OR (95% CI): 0.91 (0.68 to 1.23)
Mean change from baseline in CDAI (SD)	− 7.8 (13.8)	− 6.8 (14.2)	MD (95% CI): − 1.04 (− 2.58 to 0.50)	− 5.0 (11.9)	− 3.9 (13.6)	MD (95% CI): − 1.13 (− 2.57 to 0.31)	− 5.0 (14.0)	− 3.5 (14.0)	MD (95% CI): − 1.54 (− 3.47 to 0.39)
Mean patient-reported pain (VAS; SD)	33.2 (27.4)	36.6 (27.9)	MD (95% CI): − 3.37 (− 6.39 to − 0.34)	39.5 (27.5)	42.3 (28.3)	MD (95% CI): − 2.74 (− 5.79 to 0.32)	46.3 (28.4)	47.7 (29.0)	MD (95% CI): − 1.44 (− 5.18 to 2.30)
mACR20, *n* (%)	213 (35.9)	164 (27.8)	OR (95% CI): 1.49 (1.15 to 1.93)	142 (24.3)	123 (21.0)	OR (95% CI): 1.22 (0.92 to 1.63)	96 (24.2)	79 (20.2)	OR (95% CI): 1.27 (0.90 to 1.78)

[a] LDA: CDAI > 2.8–10; remission: CDAI ≤ 2.8

Covariates used for matched comparisons of TNFi combination versus TNFi monotherapy: gender, age, smoking status, body mass index, duration of RA, work status, insurance, patient global assessment, CDAI, prednisone use/dose and morning stiffness

CDAI Clinical Disease Activity Index, *CI* confidence interval, *Comb.* combination therapy with methotrexate, *LDA* low disease activity, *mACR20* modified American College of Rheumatology 20% response rate, *MD* mean difference, *Mono.* monotherapy, *OR* odds ratio, *RA* rheumatoid arthritis, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor, *VAS* visual analogue scale

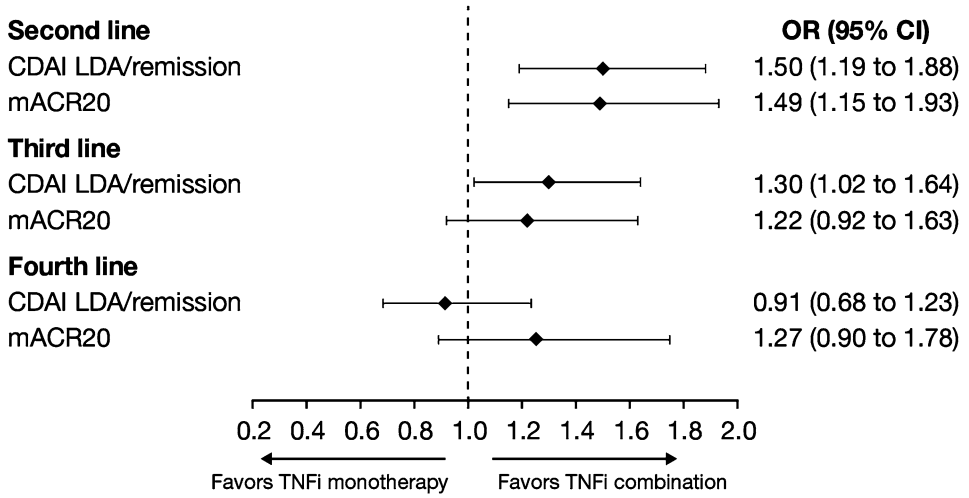

Fig. 1 Odds ratios for LDA/remission and mACR20 for TNFi combination therapy versus TNFi monotherapy. Logistic regression ORs for response rates for LDA/remission (CDAI ≤ 10) and mACR20 in patients initiating TNFi combination therapy versus TNFi monotherapy by line of therapy. LDA: CDAI > 2.8–10; remission: CDAI ≤ 2.8. Covariates used for matched comparisons of TNFi combination versus TNFi monotherapy: gender, age, smoking status, body mass index, duration of RA, work status, insurance, patient global assessment, CDAI, prednisone use/dose and morning stiffness. *CDAI* Clinical Disease Activity Index, *CI* confidence interval, *LDA* low disease activity, *mACR20* modified American College of Rheumatology 20% response rate, *OR* odds ratio, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor

Table 3 Outcomes for patients initiating tofacitinib monotherapy versus combination therapy in the third and fourth line

	Comb. (*N* = 106)	**Mono. (*N* = 106)**	**Comparison**
CDAI LDA/remission[a], *n* (%)	34 (32.1)	32 (30.2)	OR (95% CI): 1.09 (0.61 to 1.95)
Mean change from baseline in CDAI (SD)	− 3.4 (15.6)	− 2.6 (12.7)	MD (95% CI): − 0.82 (− 4.47 to 2.82)
Mean patient-reported pain (VAS; SD)	48.3 (30.5)	49.1 (28.5)	MD (95% CI): − 0.84 (− 8.75 to 7.07)
mACR20, *n* (%)	19 (17.9)	20 (19.4)	OR (95% CI): 0.87 (0.39 to 1.93)

[a] LDA: CDAI > 2.8–10; remission: CDAI ≤ 2.8

Covariates used for matched comparisons of tofacitinib combination versus tofacitinib monotherapy: race, work status, insurance, patient global assessment, and CDAI

CDAI Clinical Disease Activity Index, *CI* confidence interval, *Comb*. combination therapy with methotrexate, *LDA* low disease activity, *mACR20* modified American College of Rheumatology 20% response rate, *MD* mean difference, *Mono*. monotherapy, *OR* odds ratio, *SD* standard deviation, *VAS* visual analogue scale

initiating treatment with tofacitinib combination therapy in rates of LDA/remission (CDAI ≤ 10) (38.7 vs. 36.0%; OR [95% CI]: 1.12 [0.65 to 1.93]), mean change from baseline in CDAI (− 4.2 vs. − 3.5; MD [95% CI]: − 0.62 [− 4.57 to 3.32]), mean pain (VAS) (42.7 vs. 46.9%; MD [95% CI]: − 4.18 [− 11.72 to 3.35]), or mACR20 (21.7 vs. 17.8%; OR [95% CI]: 1.28 [0.65 to 2.53]) (Table 4 and Fig. 2). IPWRA analysis results reflected the main findings (Table S7, Online Supplementary File).

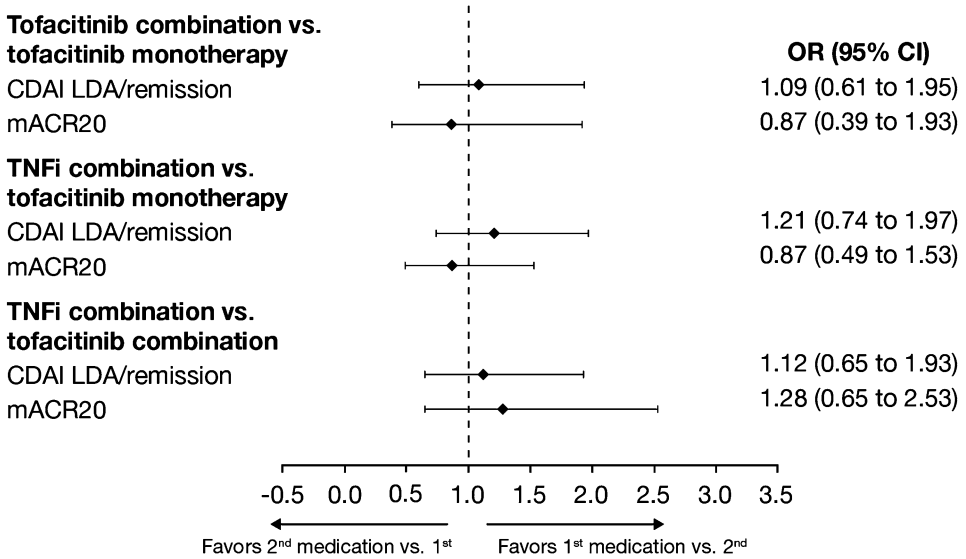

Fig. 2 Odds ratios for LDA/remission and mACR20 for TNFi or tofacitinib as monotherapy or combination therapy. Logistic regression ORs for LDA/remission (CDAI $\leq$ 10) and mACR20 for patients initiating TNFi or tofacitinib as third- or fourth-line therapy monotherapy or combination therapy. LDA: CDAI > 2.8–10; remission: CDAI $\leq$ 2.8. Covariates used for matched comparisons of tofacitinib combination versus tofacitinib monotherapy: race, work status, insurance, patient global assessment, and CDAI. Covariates used for matched comparisons of tofacitinib monotherapy versus TNFi combination therapy: gender, age, race, duration of RA, work status, smoking status, insurance, body mass index, Health Assessment Questionnaire-Disability Index, patient global assessment, CDAI, morning stiffness, history of cancer and prior number of TNFi. Covariates used for matched comparisons of tofacitinib combination therapy versus TNFi combination therapy: gender, age, duration of RA, work status, insurance, patient global assessment and morning stiffness. *CDAI* Clinical Disease Activity Index, *CI* confidence interval, *LDA* low disease activity, *mACR20* modified American College of Rheumatology 20% response rate, *OR* odds ratio, *RA* rheumatoid arthritis, *TNFi* tumor necrosis factor inhibitor

DISCUSSION

This observational study is the first of its kind to assess the comparative effectiveness of tofacitinib and TNFi (as monotherapy or in combination with MTX) for the treatment of RA in real-world clinical practice. Several RCTs have demonstrated the efficacy of TNFi [27] and tofacitinib [9–14] therapy for the treatment of RA, and the present study extends these findings into routine clinical care in the US using the data from the Corrona registry. Patients receiving second-line TNFi combination therapy with MTX achieved improved clinical outcomes compared with TNFi monotherapy; this is in line with previous observations that the addition of MTX to a TNFi regimen can improve efficacy [28–30]. Despite this, our study demonstrates that > 30% of all patients were receiving TNFi as monotherapy, with 41.7% of patients receiving TNFi as monotherapy during fourth-line treatment, which reflects findings from a previous review of data from biologic registries and US claims databases [31].

This analysis focused on the combined set of patients initiating tofacitinib as third- or fourth-line therapy, as the number of tofacitinib patients initiating first- and second-line treatment were too few for meaningful assessment. Tofacitinib appeared to be similarly effective as both monotherapy and combination therapy when used in the third or fourth line. In our analysis, tofacitinib monotherapy had similar clinical outcomes to TNFi combination therapy in the third- and fourth-line settings. To our knowledge, this is the first time this has been demonstrated using real-world data, and suggests that patients may achieve significant

Table 4 Matched analysis of outcomes for TNFi combination therapy versus tofacitinib monotherapy or tofacitinib combination therapy

	TNFi comb. (*N* = 154)	Tofacitinib mono. (*N* = 154)	Comparison	TNFi comb. (*N* = 111)	Tofacitinib comb. (*N* = 111)	Comparison
CDAI LDA/remission[a], *n* (%)	52 (33.8)	46 (29.9)	OR (95% CI): 1.21 (0.74 to 1.97)	43 (38.7)	40 (36.0)	OR (95% CI): 1.12 (0.65 to 1.93)
Mean change from baseline in CDAI (SD)	− 3.3 (15.5)	− 3.9 (12.4)	MD (95% CI): 0.58 (− 2.55 to 3.71)	− 4.2 (14.9)	− 3.5 (16.0)	MD (95% CI): − 0.62 (− 4.57 to 3.32)
Mean patient-reported pain (VAS; SD)	49.0 (27.0)	48.5 (28.7)	MD (95% CI): 0.44 (− 5.75 to 6.64)	42.7 (28.0)	46.9 (31.6)	MD (95% CI): − 4.18 (− 11.72 to 3.35)
mACR20, *n* (%)	28 (18.4)	31 (20.7)	OR (95% CI): 0.87 (0.49 to 1.53)	23 (21.7)	19.0 (17.8)	OR (95% CI): 1.28 (0.65 to 2.53)

[a] LDA: CDAI > 2.8–10; remission: CDAI ≤ 2.8

Matched analysis of outcomes for patients initiating combined third- and fourth-line therapy for TNFi combination therapy versus tofacitinib monotherapy and for TNFi combination therapy versus tofacitinib combination therapy

Covariates used for matched comparisons of tofacitinib monotherapy versus TNFi combination therapy: gender, age, race, duration of RA, work status, smoking status, insurance, body mass index, Health Assessment Questionnaire-Disability Index, patient global assessment, CDAI, morning stiffness, history of cancer and prior number of TNFi

Covariates used for matched comparisons of tofacitinib combination therapy versus TNFi combination therapy: gender, age, duration of RA, work status, insurance, patient global assessment and morning stiffness

Patient sample size varies for the TNFi combination group as they are matched against the respective tofacitinib monotherapy groups

CDAI Clinical Disease Activity Index, *CI* confidence interval, *Comb*. combination therapy with methotrexate, *LDA* low disease activity, *mACR20* modified American College of Rheumatology 20% response rate, *MD* mean difference, *Mono*. monotherapy, *OR* odds ratio, *RA* rheumatoid arthritis, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor, *VAS* visual analogue scale

efficacy with tofacitinib without the need for MTX. These results are similar to a real-world effectiveness study of patients with RA and prior use of ≥ 1 TNFi who were identified from the Corrona registry that showed no difference in the improvement of RA disease activity at 6 months (improvement in CDAI, achievement of LDA and mACR responses) between patients receiving tocilizumab as monotherapy compared with those receiving TNFi + MTX, regardless of MTX dose [32].

Approximately 60% of patients treated with combined third- and fourth-line tofacitinib received it as monotherapy. This is similar to the findings of a recent US-based database analysis, presenting data from two database sources, which found that approximately 50% of tofacitinib-treated patients received monotherapy [33]. Additionally, the ORAL Strategy RCT completed in MTX-IR patients, many of whom were naïve to advanced therapy, directly compared tofacitinib monotherapy with tofacitinib in combination with MTX (an adalimumab plus MTX arm was also assessed) [15]. ORAL Strategy could not confirm non-inferiority of the primary endpoint (ACR50 response rates at 6 months) between tofacitinib monotherapy versus either tofacitinib with MTX or adalimumab with MTX; however, ACR20 response rates (65, 73, and 71%, respectively) and CDAI-based LDA (42, 49, and 46%, respectively), as well as improvements in response rates of Health Assessment Questionnaire-Disability Index (66, 70, and 67%, respectively) at 6 months were comparable between groups.

Compared with patients who have previously received bDMARDs, patients who are bDMARD-naïve are more likely to have enhanced efficacy responses to tofacitinib [34]. It may therefore be possible that real-world studies such as the present analysis underestimate the efficacy of tofacitinib therapy, as many patients will have previously received bDMARDs. In previous clinical trials that included patients who had received prior DMARDs for treatment of RA, over 50% achieved ACR20 responses with tofacitinib monotherapy [10] or in combination with MTX [13].

This study provides observational evidence from a large, RA-specific database to enable assessment of how tofacitinib and TNFi therapies are administered in routine clinical care. This analysis complements the data obtained from clinical trials; however, it is limited by the retrospective nature of the observational study, resulting in uncertainty in regard to treatment adherence. This may partially explain the lower mACR20 response rate in the present analysis compared with ACR20 rates seen in clinical trials assessing tofacitinib and TNFi [9–15, 27]. Even so, such influence reflects the real-world considerations of clinicians.

We used propensity-score matching to minimize the bias that may occur with real-world data due to patients having differences in background disease characteristics that may skew comparisons between different treatment groups. Although this method improves comparability between the treatment groups for an 'apples to apples' matching, additional unmeasured covariates may remain unbalanced. This is a further limitation of data collected in the clinical practice setting as opposed to an RCT with randomization and tighter inclusion/exclusion criteria. Given the relatively short period of data collection and required follow-up, the number of patients receiving tofacitinib for whom appropriate data were available was lower than the population of TNFi users. In addition, some of those receiving tofacitinib had previously failed TNFi, thus limiting analyses without further line of therapy stratification. Although this study is observational, the results are consistent with RCT results that have demonstrated that tofacitinib is an effective RA treatment without MTX, particularly after inadequate response to MTX [15]. Additionally, the smaller sample size for tofacitinib initiations compared with TNFi initiations resulted in wider confidence intervals and the inability to make comparisons in the biologic-naïve population.

CONCLUSIONS

In conclusion, this study demonstrates for the first time that treatment with tofacitinib

monotherapy in the third and fourth line showed similar efficacy to either tofacitinib in combination with MTX or TNFi in combination with MTX in real-world clinical practice. Further, efficacy of TNFi when used in second-line and, to some degree, third-line settings were improved by the addition of MTX therapy. Fourth-line treatment with TNFi monotherapy did not appear to be improved by the addition of MTX. Treatment with tofacitinib monotherapy in the third and fourth line showed similar efficacy to either tofacitinib in combination with MTX or TNFi in combination with MTX.

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Compliance with Ethics Guidelines. This study was carried out in accordance with the Declaration of Helsinki. All participating investigators were required to obtain full board approval for conducting noninterventional research involving human subjects with a limited dataset. Sponsor approval and continuing review was obtained through a central Institutional Review Board (IRB), the New England Independent Review Board (NEIRB; no. 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective governing IRBs and documentation of approval was submitted to Corrona, LLC prior to the initiation of any study procedures. All patients in the registry were required to provide written informed consent and authorization prior to participating.

Data Availability. The Corrona dataset is based on a large US multicenter study adhering to a number of institutional review boards, with complex logistics. Patients did not provide consent to raw data sharing during the data collection for this purpose, and the Corrona data sharing policies do not permit raw data sharing for this purpose. An aggregated limited dataset from the current analyses is available to

qualified investigators with an approved protocol. Data requests may be sent to Corrona, represented by Dr. Jeffrey D. Greenberg MD MPH, NYU School of Sedicine, New York, NY. E-mail: jgreenberg@corrona.org.

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