Durability of Response to Tocilizumab Therapy in Rheumatoid Arthritis: Data from the US-Based Corrona Rheumatoid Arthritis Registry

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ABSTRACT

Introduction: Understanding the durability of response to treatment and factors associated with failure to maintain response in a real-world setting can inform treatment decisions for patients with rheumatoid arthritis (RA). The aim of this study was to analyze durability of response to tocilizumab (TCZ) and factors associated with durability among US patients with RA in routine clinical practice.

Methods: TCZ initiators in the Corrona RA Registry were included. Durability of response was defined as maintaining continuous TCZ treatment and either an improvement of at least minimum clinically important difference (MCID) in Clinical Disease Activity Index (CDAI) score or low disease activity (LDA). Secondary analyses included patients treated with intravenous (IV) TCZ and excluded those who discontinued TCZ without reporting reasons for discontinuation. Durability was calculated with Kaplan–Meier survival analysis. Cox proportional hazards modeling identified factors associated with durability.

Results: Among 1789 TCZ initiators, 466, 272, and 162 were persistent (with or without durable response) with follow-up visits at 1, 2, and 3 years, respectively. Median MCID durability of response in CDAI was > 50% after 36 months overall, 26 months for TCZ-IV, and > 50% after 36 months for those with known reasons for discontinuation; longer durability was associated with increased duration of RA and higher baseline CDAI score and shorter durability with history of malignancy and history of diabetes. Median LDA durability of response was 13.0 months overall, for TCZ-IV, and for those with known reasons for discontinuation; shorter durability was associated with history of malignancy, history of diabetes, and higher baseline CDAI score.

Conclusions: Median durability of response to TCZ in RA was > 3 years when defined as maintenance of MCID in CDAI score and > 1 year with the more stringent criteria of maintenance of LDA.

Trial Registration: ClinicalTrials.gov identifier, NCT01402661

Keywords: Biological therapies; Biologics; Durability of response; Real-world data; Rheumatoid arthritis; Tocilizumab

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Key Summary Points

Why carry out this study?

Using real-world data to analyze the durability of response to treatment and factors associated with failure to maintain response can inform treatment decisions for patients with rheumatoid arthritis (RA); for these patients, less is known about the durability of response to biologic therapies.

This study used real-world data to analyze the durability of response to the biologic therapy tocilizumab (TCZ) and factors associated with durability among US patients with RA.

Durability of response was defined as maintaining both continuous TCZ therapy and concurrent continuous response to therapy.

What has been learned from the study?

Among patients with RA in routine clinical practice, median durability of response to TCZ was > 3 years when measured as maintenance of minimum clinically important difference in Clinical Disease Activity Index score; even with the more stringent criteria of maintenance of low disease activity, median TCZ durability of response was > 1 year.

These results may help inform treatment decisions for patients with RA.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13622894.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting the joints; it results in chronic joint swelling, stiffness, and pain and can lead to joint damage and disability [1]. The first line of treatment for patients with RA is conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); however, to achieve the recommended goal of low disease activity (LDA) or remission, successive therapy changes are often needed [2]. Patients who do not achieve disease control with csDMARDs alone are usually treated with targeted synthetic DMARDs (tsDMARDs) or biologics [2]. There are now five families of molecular targets for RA treatment, several of which have multiple therapy options [2]. Although the efficacy of biologics in patients with RA has been extensively studied [3], less is known about the durability or maintenance of response to biologics. Understanding the durability of response to treatment and factors associated with failure to maintain response in a real-world setting can inform treatment decisions for patients with RA.

There is a critical difference between durability of response to therapy and persistency of therapy. Many studies have addressed the persistency of biologics, which is often measured as the time from treatment initiation until treatment discontinuation [4, 5]. This has been considered a proxy to therapy effectiveness, and the assumption is frequently made that the patient is responding to therapy as long as the therapy is not stopped. Maintaining a concurrent response to treatment is not taken into account in analyses evaluating persistency of biologics, csDMARDs, and tsDMARDs. In the present analysis, we evaluated the durability of response, which was defined as persistence on therapy while maintaining concurrent response to therapy. To the best of our knowledge, this approach has not previously been published for biologic treatment in patients with RA.

The present study evaluated the durability of response to tocilizumab (TCZ), a monoclonal antibody against the interleukin-6 receptor, in US patients with RA initiating TCZ in routine

clinical practice. Factors affecting durability of response were also assessed. TCZ is approved for the treatment of RA in patients with an inadequate response to DMARDs [6]; TCZ may be administered as monotherapy or in combination with other csDMARDs, and clinical studies have demonstrated that both strategies effectively reduce disease activity [7–14]. While studies have demonstrated the long-term safety, efficacy, and real-world persistence of TCZ therapy, data on the durability of response to TCZ are lacking [5, 15, 16].

METHODS

Study Setting

The Corrona RA registry is an ongoing independent, prospective, observational cohort of patients with RA (NCT01402661) [17, 18]. Patients are recruited from 193 private and academic practice sites across 42 states in the United States, with 827 participating rheumatologists. As of March 31, 2020, data on 54,453 patients with RA had been collected. Corrona's database includes information from 414,251 patient visits and 199,111 patient-years of follow-up observation time. The mean duration of patient follow-up is 4.49 years (median, 3.2 years). Ethics approval for this study was obtained from a central institutional review board (IRB; New England Independent Review Board 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 the sponsor prior to initiating any study procedures. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study Population

TCZ-naïve patients aged $\geq$ 18 years enrolled in the Corrona RA registry who initiated TCZ (subcutaneous or intravenous [IV]) after January 1, 2010, had baseline Clinical Disease Activity Index (CDAI) scores available, and had $\geq$ 1 follow-up registry visit—regardless of continuation of therapy—were included. Patients who discontinued TCZ after less than 1 month were not considered TCZ initiators because of the possibility of prescriptions being unfilled or never started. Data analyzed were collected from physician and patient questionnaires that were completed during routine clinical encounters over the study period. The Corrona Registry has been previously described in detail elsewhere [17]. Data collected during participation in the registry include patient demographics, clinical characteristics, history of comorbidities, current and prior medication use, clinical disease activity measures, and patient-reported outcomes [17]. Durability of response at 1, 2, and 3 years was assessed in patients who were persistent on medication and who had a follow-up visit at these time points so that disease activity could be measured. Persistency at 1, 2, or 3 years did not require follow-up visits (or disease activity evaluation) at these time points, as a later visit could be used to infer persistency at earlier timepoints (i.e., a patient who had a follow-up visit at year 3 and was receiving the medication, but who did not have a visit at year 2, was considered persistent at years 2 and 3).

Study Design and Outcomes

This observational study evaluated the durability of response and factors associated with decreased durability in patients with RA initiating TCZ. Durability of response was defined as maintaining continuous TCZ and 1 of the following: (a) continuous maintenance of at least a minimum clinically important difference (MCID) in CDAI score, defined as an improvement in CDAI score of $\geq$ 2 if the baseline was $\leq$ 10, $\geq$ 6 if the baseline was > 10 to $\leq$ 22, and $\geq$ 11 if the baseline was > 22 [19] or (b) continuous maintenance of at least LDA

(CDAI ≤ 10). Patient response was no longer durable upon the first discontinuation of TCZ or the first failure to maintain MCID in CDAI score or LDA. The primary outcome was the durability of response up to 36 months and factors associated with decreased durability in all TCZ initiators. Secondary analyses estimated durability after (a) including only those who were treated with TCZ-IV or (b) excluding patients without a reported reason for discontinuing TCZ (patients with safety- or efficacy-related reasons for discontinuation were defined as failing to maintain durability, whereas nonmedical reasons for discontinuation [e.g., insurance coverage] were censored at the time of discontinuation).

Statistical Analyses

Baseline characteristics were summarized using means and SDs for continuous variables and frequencies and percentages for categorical variables. Kaplan–Meier product-limit estimates of survival were used to estimate durability.

Factors associated with durability were identified through Cox proportional hazards modeling.

RESULTS

A total of 1789 TCZ initiators with ≥ 1 follow-up visit were identified (Fig. 1). The mean (SD) time between follow-up visits (after TCZ initiation) was 6.7 (4.4) months. Among the 1789 TCZ initiators, 81.0% were female, 85.0% were white, and 75.4% were overweight or obese (Table 1). The mean (SD) age was 58.5 (12.6) years, duration of RA was 12.0 (9.6) years, and CDAI score was 23.2 (14.2). Most patients (93.4%) had previously received biologics, and 67.4% had received ≥ 2 prior biologics. Overall, 38.1% initiated TCZ as monotherapy. Secondary analyses included 1284 patients who initiated TCZ-IV and 1303 patients with known reasons for discontinuing TCZ (patients with safety- or efficacy-related reasons for discontinuation were defined as failing to maintain
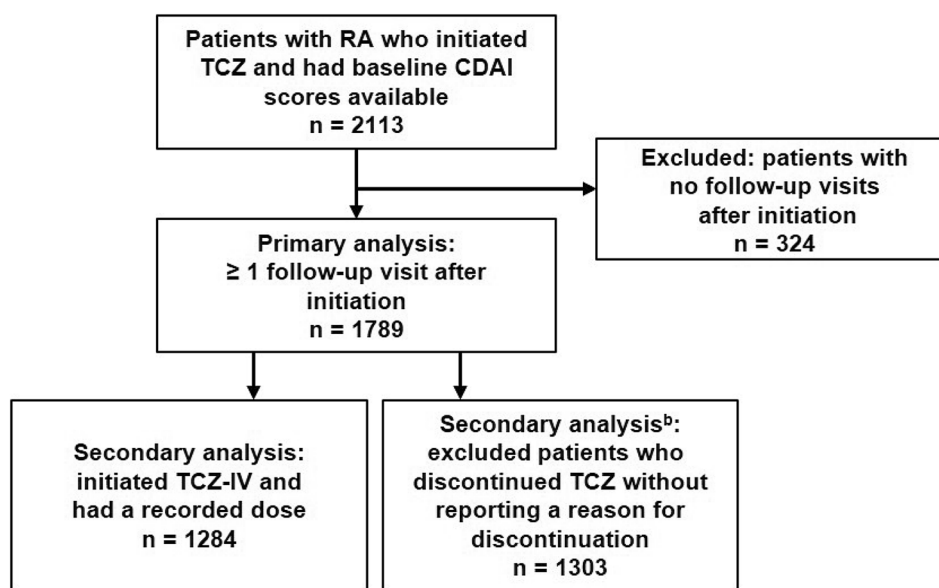

Fig. 1 Selection of eligible patients for analysis.[a] *CDAI* Clinical Disease Activity Index, *IV* intravenous, *RA* rheumatoid arthritis, *TCZ* tocilizumab. [a]Patients selected using the January 31, 2019, version of the Corrona RA database. [b]Patients with safety- or efficacy-related reasons for discontinuation were defined as failing to maintain durability, whereas nonmedical reasons for discontinuation [e.g., insurance coverage] were censored at the time of discontinuation

Table 1 Baseline patient characteristics

	TCZ Initiators (N = 1789)
Female, n (%)	1449 (81.0)
Age, mean (SD), years	58.5 (12.6)
Duration of RA, mean (SD), years	12.0 (9.6)
White, n (%)	1512 (85.0)
Previous or current smoker, n (%)[a]	873 (49.1)
BMI category, n (%)	
Underweight/normal weight (< 25 kg/m^2)	439 (24.5)
Overweight (≥ 25 to < 30 kg/m^2)	524 (29.3)
Obese (> 30 kg/m^2)	825 (46.1)
Insurance, n (%)[b]	
None	11 (0.6)
Private	1322 (73.9)
Medicaid	92 (5.1)
Medicare	681 (38.1)
History of comorbid conditions, n (%)	
Hypertension	596 (33.3)
Diabetes	185 (10.3)
Malignancy[c]	110 (6.1)
CVD[d]	736 (41.1)
Medication history	
Prior csDMARD use, n (%)[e]	
0	87 (4.9)
1	616 (34.4)
≥ 2	1086 (60.7)
Prior TNFi use, n (%)[e]	
0	209 (11.7)
1	673 (37.6)
≥ 2	907 (50.7)
Prior non-TNFi use, n (%)[e]	
0	867 (48.5)

Table 1 continued

	TCZ Initiators (N = 1789)
1	712 (39.8)
≥ 2	210 (11.7)
Prior biologic use, n (%)[e]	
0	118 (6.6)
1	466 (26.0)
≥ 2	1205 (67.4)
Concomitant medication, n (%)	
Monotherapy	682 (38.1)
Combination with csDMARDs	1107 (61.9)
Prednisone use, n (%)	623 (34.8)
Disease activity	
Tender joint count (0–28), mean (SD)	8.4 (7.7)
Swollen joint count (0–28), mean (SD)	5.9 (5.5)
Physician global assessment (0–100), mean (SD)	39.2 (22.9)
Patient global assessment (0–100), mean (SD)	51.0 (25.8)
CDAI (0–76), mean (SD)	23.2 (14.2)
Patient pain (0–100), mean (SD)	53.6 (26.7)
mDAS (1.69–8.75), mean (SD)	4.7 (1.4)
mHAQ (0–3), mean (SD)	0.6 (0.5)
Patient fatigue (0–100), mean (SD)	54.8 (28.3)
Morning stiffness, n (%)	1586 (89.3)

BMI body mass index, *CDAI* Clinical Disease Activity Index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *CVD* cardiovascular disease, *mDAS* modified Disease Activity Score, *mHAQ* modified Health Assessment Questionnaire, *RA* rheumatoid arthritis, *TCZ* tocilizumab, *TNFi* tumor necrosis factor inhibitor

[a] n = 1777

[b] Totals may not add up to 100% because patients may have ≥ 1 type of insurance

[c] Malignancy includes breast cancer, lung cancer, lymphoma, skin cancer (melanoma and squamous cell), and other cancers

[d] History of CVD includes history of cardiac revascularization procedure (coronary artery bypass grafting, stent, angioplasty), ventricular arrhythmia, cardiac arrest, myocardial infarction, acute coronary syndrome, unstable angina, other coronary artery disease, congestive heart failure (with and without hospitalization), stroke, transient ischemic attack, other cardiovascular, deep vein thrombosis, peripheral arterial disease, pulmonary embolism, and carotid artery disease

[e] Including past and current therapies. csDMARDs: methotrexate, hydroxychloroquine, leflunomide, sulfasalazine, azathioprine, minocycline, and cyclosporine. TNFis: adalimumab, etanercept, certolizumab pegol, golimumab, and infliximab. Non-TNFis: sarilumab, abatacept, and rituximab (tocilizumab excluded). Biologics: adalimumab, etanercept, certolizumab pegol, golimumab, infliximab, sarilumab, abatacept, rituximab, and tofacitinib
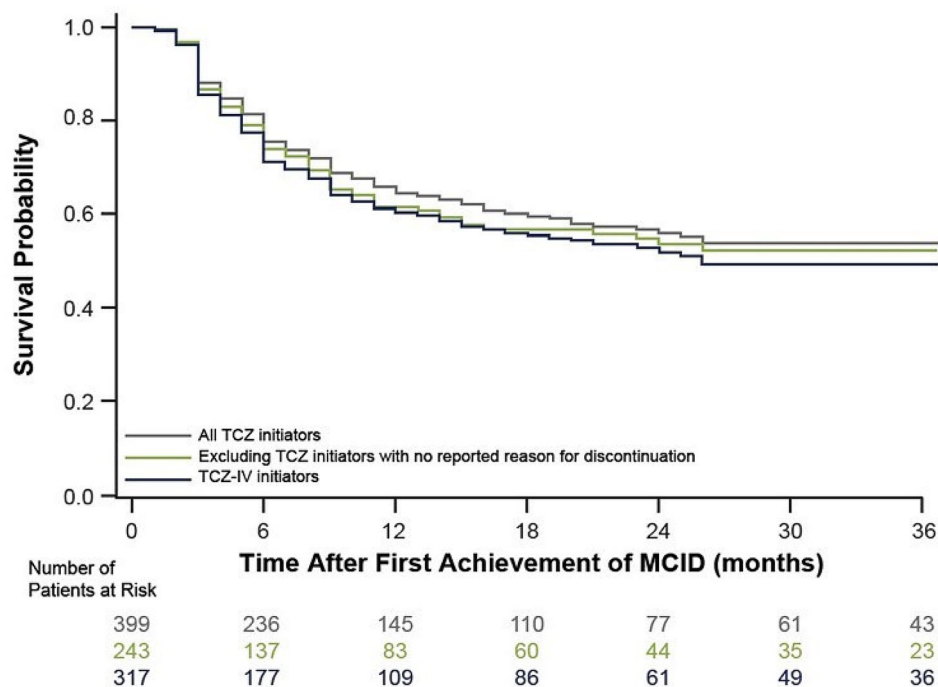
Fig. 2 Kaplan–Meier plots of MCID durability of response among patients who achieved MCID. *IV* intravenous, *MCID* minimum clinically important difference, *TCZ* tocilizumab

durability, whereas nonmedical reasons for discontinuation [e.g., insurance coverage] were censored at the time of discontinuation). At 1, 2, and 3 years, 861, 483, and 298 patients were persistent (on therapy with or without durable response), respectively. Among these patients, 466, 272, and 162 had follow-up visits at 1, 2, and 3 years, respectively.

MCID Durability of Response

With the Kaplan–Meier estimate of the survival function among all TCZ initiators who achieved MCID in CDAI, durability of response, measured by continuous TCZ and maintenance of MCID, remained > 50% after 36 months of follow-up (Fig. 2); the precise median (95% CI) MCID durability was not estimable (NE) because the survival rate was > 50%. For these patients, the proportion (95% CI) maintaining MCID durability at 1, 2, and 3 years was 64.4% (59.2–69.6%), 56.0% (50.0–62.0%), and 51.8% (44.7–58.9%), respectively. For TCZ-IV initiators who achieved MCID in CDAI score, median

(95% CI) MCID durability of response was 26 (17–NE) months (Fig. 2). The estimation of the upper confidence limit was NE because, due to a lack of events, the survival estimate did not drop to a low enough level prior to the end of study follow-up. At 1, 2, and 3 years, the proportion of patients (95% CI) maintaining MCID durability was 60.2% (54.2–66.2%), 51.9% (45.2–58.6%), and 47.4% (39.8–55.0%), respectively, among these patients. Among patients with known reasons for discontinuation who achieved MCID, median (95% CI) MCID durability of response was 45 (16–NE) months (Fig. 2). For these patients, the proportion (95% CI) maintaining MCID durability was 60.8% (53.8–67.7%), 53.5% (45.7–61.3%), and 49.0% (39.3–58.7%) at 1, 2, and 3 years, respectively.

Among all TCZ initiators who achieved MCID, longer MCID durability of response (hazard ratio [HR]; 95% CI) was associated with increased duration of RA (0.91 [0.83–0.99]; $p = 0.04$) and higher baseline CDAI score (0.72 [0.60–0.87]; $p = 0.001$); factors associated with shorter MCID durability included history of malignancy (2.88 [1.57–5.27]; $p = 0.001$) and
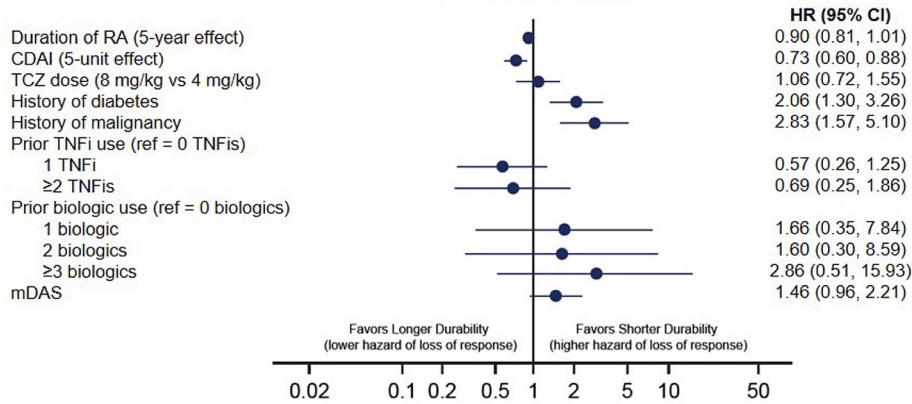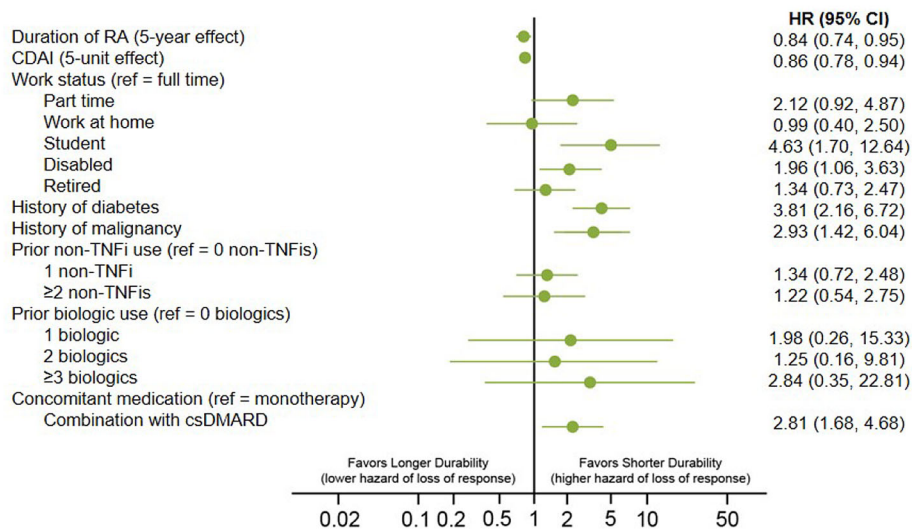
A

All TCZ Initiators

	HR (95% CI)
Duration of RA (5-year effect)	0.91 (0.83, 0.99)
CDAI (5-unit effect)	0.72 (0.60, 0.87)
Work status (ref = full time)	
Part time	1.59 (0.85, 2.97)
Work at home	1.44 (0.77, 2.69)
Student	2.07 (0.89, 4.82)
Disabled	1.54 (0.94, 2.51)
Retired	1.21 (0.74, 1.98)
History of diabetes	1.89 (1.19, 3.00)
History of malignancy	2.88 (1.57, 5.27)
Prior TNFi use (ref = 0 TNFis)	
1 TNFi	0.65 (0.34, 1.23)
≥2 TNFis	0.98 (0.53, 1.81)
Prior non-TNFi use (ref = 0 non-TNFis)	
1 non-TNFi	1.40 (0.95, 2.06)
≥2 non-TNFis	1.70 (1.00, 2.90)
mDAS	1.35 (0.91, 2.02)

Favors Longer Durability (lower hazard of loss of response)   Favors Shorter Durability (higher hazard of loss of response)

0.1 0.2   0.5   1   2   5 10

B

TCZ-IV Initiators

	HR (95% CI)
Duration of RA (5-year effect)	0.90 (0.81, 1.01)
CDAI (5-unit effect)	0.73 (0.60, 0.88)
TCZ dose (8 mg/kg vs 4 mg/kg)	1.06 (0.72, 1.55)
History of diabetes	2.06 (1.30, 3.26)
History of malignancy	2.83 (1.57, 5.10)
Prior TNFi use (ref = 0 TNFis)	
1 TNFi	0.57 (0.26, 1.25)
≥2 TNFis	0.69 (0.25, 1.86)
Prior biologic use (ref = 0 biologics)	
1 biologic	1.66 (0.35, 7.84)
2 biologics	1.60 (0.30, 8.59)
≥3 biologics	2.86 (0.51, 15.93)
mDAS	1.46 (0.96, 2.21)

Favors Longer Durability (lower hazard of loss of response)   Favors Shorter Durability (higher hazard of loss of response)

0.02   0.1 0.2 0.5 1 2   5 10   50

C

TCZ Initiators Excluding Those with No Reported Reason for Discontinuation

	HR (95% CI)
Duration of RA (5-year effect)	0.84 (0.74, 0.95)
CDAI (5-unit effect)	0.86 (0.78, 0.94)
Work status (ref = full time)	
Part time	2.12 (0.92, 4.87)
Work at home	0.99 (0.40, 2.50)
Student	4.63 (1.70, 12.64)
Disabled	1.96 (1.06, 3.63)
Retired	1.34 (0.73, 2.47)
History of diabetes	3.81 (2.16, 6.72)
History of malignancy	2.93 (1.42, 6.04)
Prior non-TNFi use (ref = 0 non-TNFis)	
1 non-TNFi	1.34 (0.72, 2.48)
≥2 non-TNFis	1.22 (0.54, 2.75)
Prior biologic use (ref = 0 biologics)	
1 biologic	1.98 (0.26, 15.33)
2 biologics	1.25 (0.16, 9.81)
≥3 biologics	2.84 (0.35, 22.81)
Concomitant medication (ref = monotherapy)	
Combination with csDMARD	2.81 (1.68, 4.68)

Favors Longer Durability (lower hazard of loss of response)   Favors Shorter Durability (higher hazard of loss of response)

0.02   0.1 0.2 0.5 1 2   5 10   50

◀**Fig. 3** Estimated effects of covariates on MCID durability of response. *CDAI* Clinical Disease Activity Index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *IV* intravenous, *MCID* minimum clinically important difference, *mDAS* modified Disease Activity Score, *RA* rheumatoid arthritis, *Ref* reference, *TCZ* tocilizumab, *TNFi* tumor necrosis factor inhibitor

history of diabetes (1.89 [1.19–3.00]; *p* = 0.01) (Fig. 3a). For TCZ-IV initiators, longer MCID durability (HR [95% CI]) was associated with higher baseline CDAI score (0.73 [0.60–0.88]; *p* = 0.001), whereas history of malignancy (2.83 [1.57–5.10]; *p* = 0.001) and history of diabetes (2.06 [1.30–3.26]; *p* = 0.002) were associated with shorter MCID durability (Fig. 3b). When including only patients with known reasons for discontinuation, longer MCID durability (HR [95% CI]) was associated with increased duration of RA (0.84 [0.74–0.95]; *p* = 0.01) and higher baseline CDAI score (0.86 [0.78–0.94]; *p* = 0.001); factors associated with shorter MCID durability included history of malignancy (2.93

[1.42–6.04]; *p* = 0.004) and history of diabetes (3.81 [2.16–6.72]; *p* < 0.0001) (Fig. 3c).

LDA Durability of Response

With the Kaplan–Meier estimate of the survival function among all TCZ initiators who achieved LDA, the median (95% CI) LDA durability of response, defined by continuous TCZ and maintenance of LDA, was 13.0 (12.0–20.0) months (Fig. 4). For these patients, the proportion (95% CI) maintaining LDA durability at 1, 2, and 3 years was 52.3% (45.7–59.0%), 37.6% (30.2–45.0%), and 27.3% (18.2–36.4%), respectively. Among TCZ-IV initiators who achieved LDA, median (95% CI) LDA durability was 13.0 (10.0–19.0) months (Fig. 4). At 1, 2, and 3 years, the proportion of patients (95% CI) maintaining LDA durability was 50.8% (43.3–58.3%), 34.9% (26.6–43.1%), and 26.0% (16.2–35.8%), respectively, among the TCZ-IV patients who achieved LDA. Among patients with known reasons for discontinuation who achieved LDA, median (95% CI) LDA durability was 13.0 (9.0–29.0) months (Fig. 4). For these patients,
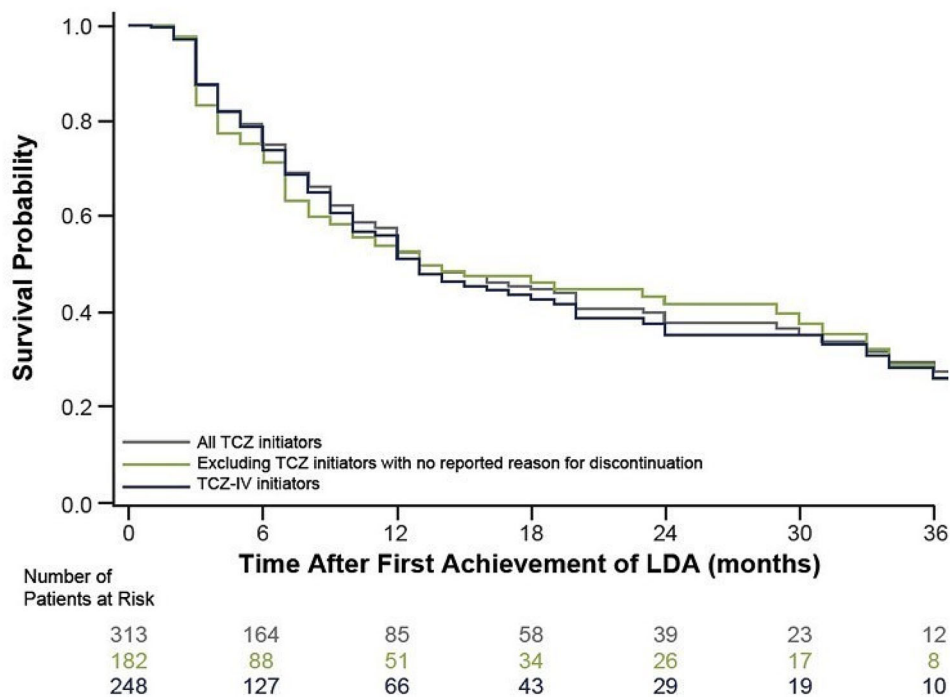
Fig. 4 Kaplan–Meier plots of LDA durability of response among patients who achieved LDA. *IV* intravenous, *LDA* low disease activity, *TCZ* tocilizumab

the proportion (95% CI) maintaining LDA durability was 52.6% (44.1–61.2%), 41.5% (32.0–50.9%), and 25.7% (13.7–37.6%) at 1, 2, and 3 years, respectively.

Among all TCZ initiators who achieved LDA, factors associated with shorter LDA durability (HR [95% CI]) included history of malignancy (2.83 [1.66–4.82]; $p = 0.0001$), history of diabetes (1.69 [1.03–2.77]; $p = 0.04$), and higher baseline CDAI score (1.11 [1.05–1.17]; $p = 0.001$) (Fig. 5a). For TCZ-IV initiators, shorter LDA durability (HR [95% CI]) was associated with history of malignancy (2.92 [1.65–5.15]; $p = 0.0002$), history of diabetes (1.80 [1.08–3.00]; $p = 0.02$), and higher baseline CDAI score (1.10 [1.03–1.17]; $p = 0.004$) (Fig. 5b). When only patients with known reasons for discontinuation were included, factors associated with shorter LDA durability (HR [95% CI]) included history of malignancy (2.57 [1.37–4.80]; $p = 0.003$) and higher baseline CDAI score (1.14 [1.06–1.23]; $p = 0.001$) (Fig. 5c).

DISCUSSION

This study evaluated durability of response to TCZ therapy, defined as continuous therapy with concurrent maintenance of disease activity response, in US TCZ-naïve patients with RA in clinical practice. This study also assessed factors associated with durability. Durability of response was measured in two ways: (a) as continuous TCZ and maintenance of at least MCID in CDAI score or (b) as continuous TCZ and maintenance of at least LDA. Such an evaluation of therapy effectiveness, including both persistence on therapy as well as maintenance of concurrent response to treatment in a single outcome, has not to our knowledge previously been reported for biologic therapy in patients with RA. Multiple large registry studies have evaluated drug retention separately from change in disease activity measures over time [20, 21]. Using the aforementioned definition of durability, the present study observed a median durability of response to TCZ therapy of > 3 years when measured as maintenance of MCID; even with the more stringent criteria of

maintenance of LDA, durability of response was > 1 year.

Persistence on therapy, which has been studied for biologics in RA [4, 5], has been considered indirect evidence of response to treatment, but this is not always accurate because patients may continue treatment despite having uncontrolled disease activity [22, 23]. In a behavioral intervention trial of treat-to-target care in RA, treatment was not accelerated despite disease activity measures not being met (CDAI > 10) at approximately 47% of patient visits, and barriers to accelerating treatment included patient reluctance and medication lag time [22]. Patient preference was also observed as a barrier to adjusting treatment in a randomized controlled study of implementing the treat-to-target approach in RA [23]. These studies demonstrated that persistence on therapy is not always sufficient to indicate effectiveness of medications and does not reflect continuous response of disease activity.

Persistency data reported in the literature do not account for concurrent response to treatment, as is done in the present study; this may explain discrepancies between results reported in the existing literature and what is reported here. A large, observational study in patients with RA in Canada found that, over a mean (SD) follow-up of 1.9 (1.6) years, 38.7% of patients discontinued biologics [24]. This included patients discontinuing for ineffectiveness (20.3%), adverse events (8.1%), and other reasons (10.3%). A US administrative claims study of patients with RA initiating biologics demonstrated that the unadjusted probability of TCZ persistence, defined as time to therapy switch or discontinuation, was 51.5% 1 year after initiation and 38.8% 2 years after initiation [5]. It is also important to note that the present study analyzed durability of response among patients who achieved MCID or LDA, whereas other studies examined the persistence among all patients; this needs to be taken into account when comparing these findings.

To better inform treatment decisions for patients with RA, baseline characteristics were analyzed to determine if they were associated with durability of TCZ therapy. Our analysis indicated that higher baseline CDAI score and
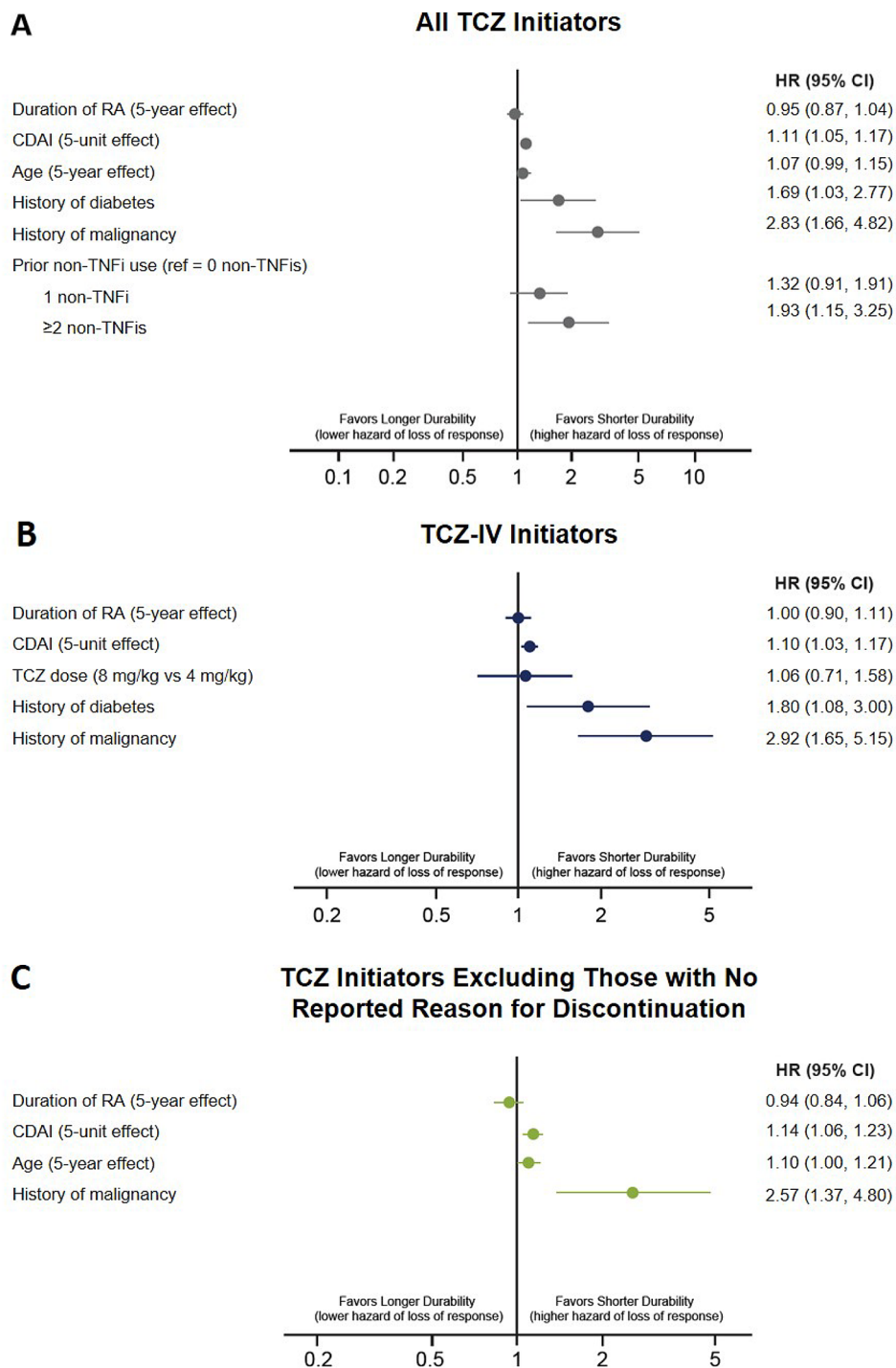
Fig. 5 Estimated effects of covariates on LDA durability of response. *CDAI* Clinical Disease Activity Index, *IV* intravenous, *LDA* low disease activity, *RA* rheumatoid arthritis, *Ref* reference, *TCZ* tocilizumab, *TNFi* tumor necrosis factor inhibitor

duration of RA were associated with longer MCID durability, and no factors associated with longer LDA durability were identified. Perhaps

this association between higher baseline disease activity and MCID improvement may be explained by the fact that it is feasible to have

greater improvement with higher baseline disease activity. Higher baseline CDAI score was also associated with shorter LDA durability. Since LDA is a more stringent criterion of response than MCID, it is to be expected that these two measures of disease activity would not have the same association with baseline CDAI score. It is likely easier to achieve and maintain MCID than LDA. For example, if a patient's CDAI score improves from 30 to 15, they have achieved MCID but not LDA. Furthermore, a patient could achieve LDA at one visit but at the next visit their CDAI score could increase slightly, which puts them outside the range for achieving LDA but still within range for MCID. Thus, for patients with higher baseline CDAI scores, maintenance of MCID may be more achievable than maintenance of LDA.

Shorter durability was associated with history of malignancy and history of diabetes in analyses of both MCID and LDA durability; however, these represented small subgroups of the overall study population (6.1 and 10.3%, respectively), and the underlying reasons for these associations are not clear. Studies have shown that treatment with TCZ is not associated with malignancy or diabetes. In a post hoc analysis of five phase 3 trials and long-term extension studies of TCZ in patients with RA, adjudicated malignancy rates among those who received TCZ with or without methotrexate or DMARDs were not greater than rates among those who received placebo and methotrexate or DMARDs; in the TCZ all-exposure population, rates remained consistent over time [25]. Patients with RA receiving TCZ treatment were shown to have lower glycated hemoglobin A1c levels after TCZ initiation, and treatment with TCZ was found to improve insulin sensitivity [26, 27]. Shorter LDA durability was also associated with higher baseline CDAI score.

This study has some limitations inherent to observational studies. The generalizability of the data to broader patient populations is a potential limitation. However, patients from diverse backgrounds are represented in the Corrona RA Registry, as there are participating practices in academic, private, rural, and urban settings. Additionally, generalizability of the registry data has been supported by a study showing that among US patients with RA covered by Medicare, baseline characteristics of patients in the Corrona RA Registry were comparable to those of the general population [18]. It is possible that patients could have intermittently been out of LDA or MCID between study visits. Use of the Corrona RA Registry enabled a large patient population to be included, which is a strength of this study.

CONCLUSIONS

In this real-world RA population who initiated TCZ, most patients received ≥ 2 prior biologics. Median durability of response was > 3 years when measured as maintenance of at least MCID in CDAI score while receiving therapy with TCZ; even with the more stringent criteria of maintenance of LDA, durability of response was > 1 year. Understanding durability of response to TCZ may help inform treatment decisions for patients with RA.

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