Effectiveness of Tocilizumab in Patients with Rheumatoid Arthritis Is Unaffected by Comorbidity Burden or Obesity: Data from a US Registry

Dimitrios A. Pappas¹, Carol J. Etzel², Margaux Crabtree², Taylor Blachley², Jennie Best³, Steve Zlotnick³, and Joel M. Kremer⁴

ABSTRACT. *Objective.* Comorbidity burden and obesity may affect treatment response in patients with rheumatoid arthritis (RA). Few real-world studies have evaluated the effect of comorbidity burden or obesity on the effectiveness of tocilizumab (TCZ). This study evaluated TCZ effectiveness in treating RA patients with high versus low comorbidity burden and obesity versus nonobesity in US clinical practice.

Methods. Patients in the Corrona RA registry who initiated TCZ were stratified by low or high comorbidity burden using a modified Charlson Comorbidity Index (mCCI) and by obese or nonobese status using body mass index (BMI). Improvements in disease activity and functionality after TCZ initiation were compared for the above strata of patients at 6 and 12 months after adjusting for statistically significant differences in baseline characteristics.

Results. We identified patients with high (mCCI ≥ 2 ; $n = 195$) and low (mCCI < 2 ; $n = 575$) comorbidity burden and patients categorized as obese (BMI ≥ 30 ; $n = 356$) and nonobese (BMI < 30 ; $n = 449$) who were treated with TCZ. Most patients ($> 95\%$) were biologic experienced and about one-third of patients received TCZ as monotherapy, with no significant differences between patients by comorbidity burden or obesity status. Improvement in disease activity and functionality at 6 and 12 months was similar between groups, regardless of comorbidity burden or obesity status.

Conclusion. In this real-world analysis, TCZ was frequently used to treat patients with high comorbidity burden or obesity. Effectiveness of TCZ did not differ by comorbidity or obesity status.

Key Indexing Terms: comorbidity, obesity, registry, rheumatoid arthritis, tocilizumab

Rheumatoid arthritis (RA) is a chronic autoimmune disease that leads to inflammation and progressive destruction of synovial joints. Comorbid conditions are more common, often more severe, and less well-managed in patients with RA compared with the general population^{1,2}. Higher comorbidity burden is associated with a higher degree of disease activity and physical disability and a poorer health-related quality of life^{3,4}. In addition, higher comorbidity burden was reported to impair response to treatment in patients with RA⁵. One common comorbidity, obesity, is more prevalent in patients with RA than

in the general population^{6,7}. Obese patients with RA often have higher disease activity⁸ and poorer responses to therapy than nonobese patients^{9,10,11,12,13}.

Tocilizumab (TCZ) is a humanized monoclonal antibody against the interleukin 6 receptor approved for patients with moderate to severe RA¹⁴. Although caution should be used in patients with diverticulitis, chronic or recurrent infections, neutropenia, or thrombocytopenia, the existence of prior comorbidities does not contraindicate its use¹⁴. The dose of TCZ can be adjusted based on patient weight. Few studies have investigated

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¹D.A. Pappas, MD, Columbia University, New York, New York; Corrona, LLC, Waltham, Massachusetts; ²C.J. Etzel, PhD, M. Crabtree, MPH, T. Blachley, MS, Corrona, LLC, Waltham, Massachusetts; ³J. Best, PhD, S. Zlotnick, PharmD, Genentech, Inc., South San Francisco, California; ⁴J.M. Kremer, MD, Albany Medical College and The Center for

Rheumatology, Albany, New York, USA.

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Address correspondence to Dr. D.A. Pappas, Columbia University, College of Physicians and Surgeons, New York Presbyterian Hospital, P&S Building, Suite 10-455, New York, NY 10032, USA. Email: dpappas@corrona.org.

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the use of TCZ in patients with high comorbidity burden or obesity and their effect on the effectiveness of TCZ in routine clinical practice^{15,16}. This analysis evaluated the clinical response to TCZ in patients with RA stratified by comorbidity burden and obesity.

MATERIALS AND METHODS

Study setting. The Corrona RA registry is an ongoing, independent, prospective, observational cohort of patients with RA (ClinicalTrials.gov: NCT01402661)^{17,18} and has been previously described¹⁸. Patients are recruited from 174 private and academic practice sites across 41 states in the United States, with 686 participating rheumatologists. As of March 31, 2018, data on 48,535 patients with RA were collected. The Corrona database includes 367,457 patient visits and about 169,968 patient-years of follow-up observation time. The mean duration of patient follow-up is 4.30 years (median 3.35 yrs).

Patient population. This study included patients with RA aged ≥ 18 years in the Corrona registry who initiated TCZ between January 1, 2010, and October 31, 2017, and had follow-up visits at 6 and 12 months (± 2 mos) after initiation, regardless of whether TCZ was continued for the entire follow-up period. For analysis inclusion, patients must have had baseline body mass index (BMI) available and the necessary data for a modified Charlson Comorbidity Index (mCCI) score.

The study was conducted according to the current version of the Declaration of Helsinki. Ethics approvals were obtained from the New England Independent Review Board (IRB; no. 120160610) for private practice sites and the local IRB of participating academic sites. All patients provided written informed consent.

Study design and outcomes. This was a retrospective study to evaluate the use of TCZ and to determine whether the effectiveness of TCZ differs in obese versus nonobese patients and high versus low comorbidity burden at baseline.

For comorbidity burden, patients were stratified into low versus high comorbidity burden groups by mCCI. CCI is a weighted index of comorbid conditions that functions as a predictor of mortality¹⁹. The mCCI was calculated as the sum of prior (history of) physician-reported comorbid conditions in the Corrona registry, including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, diabetes mellitus, leukemia, lymphoma, solid-tumor cancer (excluding nonmelanoma of the skin), and liver disease. Conditions that were not captured and were excluded from mCCI score include dementia, kidney disease, hemiplegia, and acquired immunodeficiency syndrome. The CCI includes connective tissue disease, which was coded as 1 for all participants, because the population was limited to patients with RA. Low comorbidity burden was an mCCI score of < 2 and high comorbidity burden was an mCCI score of ≥ 2 .

To assess the effect of obesity, patients were stratified into the nonobese group if BMI was < 30 and into the obese group if BMI was ≥ 30 . BMI and mCCI were calculated at the time of TCZ initiation.

Outcomes were evaluated at 6 and 12 months post-TCZ initiation; ± 2 months was allowed in order to classify a visit as a 6- or 12-month follow-up visit. The primary endpoint was mean change in Clinical Disease Activity Index (CDAI) from baseline to 6 months and from baseline to 12 months. Secondary endpoints were evaluated at the same timepoints and included TCZ dose, mean change in Health Assessment Questionnaire (HAQ) score, the proportion of patients who achieved low disease activity (LDA; CDAI ≤ 10), and patients with change greater than or equal to the minimum clinically important difference (MCID) in CDAI and HAQ. MCID for CDAI was calculated based on baseline CDAI (if CDAI ≤ 10 at baseline, then MCID = 2; if CDAI > 10 to ≤ 22 at baseline, then MCID = 6; if CDAI > 22 at

baseline, then MCID = 11)²⁰. MCID for HAQ was defined as a reduction from baseline ≥ 0.22 ²⁰.

Statistical analysis. Patients were categorized based on mCCI (high vs low comorbidity burden) and BMI (obese vs nonobese). Baseline demographics, clinical characteristics, disease activity, and treatment history were described for all patient categories. Standardized differences were calculated between high versus low mCCI and obese versus nonobese patients to identify statistically significant differences at baseline (time of TCZ initiation).

Outcomes at 6 and 12 months were compared in both unadjusted and adjusted analyses. Baseline characteristics with an absolute standardized difference > 0.1 were identified as covariates for inclusion in adjusted comparisons. Outcomes were compared between cohorts using 2-sample *t* tests or chi-square tests in unadjusted analyses, and linear or logistic regression models in adjusted analyses.

For patients who discontinued TCZ but did not switch to another biologic prior to the 6- or 12-month follow-up visit, outcomes at the 6- and 12-month visits were included as observed. For patients who discontinued TCZ and switched to a different biologic prior to the 6- or 12-month follow-up visit, disease activity and patient-reported outcomes (PRO) at the time of switch were used as the 6- or 12-month endpoints (last observation on TCZ carried forward) for evaluation of continuous outcomes, and nonresponse was imputed for analysis of binary outcomes.

RESULTS

Patient baseline characteristics by comorbidity burden. Of 805 patients who initiated TCZ, 770 had mCCI data available at baseline; 575 patients (74.7%) had a low mCCI, and 195 (25.3%) had a high mCCI. As shown in Table 1B, over 95% of patients were biologic experienced, and about one-third received TCZ monotherapy. Most patients (93.8%) received intravenous (IV) TCZ (Supplementary Table 1, available with the online version of this article). Of the 706 patients (93.8% of all initiators) who received IV TCZ, 528 (74.7%) had a low mCCI and 178 (25.2%) had a high mCCI. Among all IV TCZ initiators, 407 (57.6%) had baseline dose information [low mCCI: 316 (59.8%); high mCCI: 91 (51.1%)]. Of IV TCZ initiators with dose available ($n = 407$), 230 (56.5%) received 4 mg/kg [low mCCI: 172 (54.4%); high mCCI: 58 (63.7%)] and 177 (43.5%) received 8 mg/kg [low mCCI: 144 (45.6%); high mCCI: 33 (36.3%)]. Of the 47 (6.1% of all initiators) patients who initiated subcutaneous (SC) TCZ, 36 (76.6%) had a low mCCI and 11 (23.4%) had a high mCCI. Of SC TCZ initiators, 30 (63.8%) had baseline dose frequency available [low mCCI: 26 (72.2%); high mCCI: 4 (36.4%)]. Of SC TCZ initiators with dose available ($n = 30$), 13 (43.3%) received TCZ every 2 weeks [low mCCI: 10 (38.5%); high mCCI: 3 (75.0%)] and 17 (56.7%) received TCZ every week [low mCCI: 16 (61.5%); high mCCI: 1 (25.0%)].

Compared with patients with mCCI < 2 , patients with mCCI ≥ 2 were older [mean (SD) age, 56.9 (13.1) vs 61.5 (12.3) yrs], more likely to be obese (41.7% vs 52.8%), had a longer mean (SD) disease duration [11.6 (8.9) vs 12.8 (9.9) yrs], and had higher mean (SD) baseline HAQ scores [0.6 (0.5) vs 0.7 (0.6); Table 1A–B]. Baseline mean CDAI was in the high disease activity range in both subgroups but was higher in patients with a high mCCI [mean (SD) 23.9 (13.9) vs 25.7 (13.4)].

Among patients with a high mCCI score, the mean (SD)

Table 1A. Patient demographics at baseline among patients with low versus high comorbidity burden who initiated TCZ.

Characteristic	Low Burden (mCCI < 2), n = 575	High Burden (mCCI ≥ 2), n = 195	Standardized Difference
Female, n (%)	466 (81.0)	151 (77.4)	−0.089
Age, yrs, mean (SD)	56.9 (13.1)	61.5 (12.3)	0.362
Duration of RA, yrs, mean (SD)	11.6 (8.9)	12.8 (9.9)	0.132
Race, n (%)			
White	510 (88.7)	180 (92.3)	0.123
Black/African American	28 (4.9)	9 (4.6)	−0.012
Asian	13 (2.3)	3 (1.5)	−0.053
Other	24 (4.2)	3 (1.5)	−0.159
Education (college or above), n (%)	352 (61.4)	108 (56.0)	−0.111
Smoking status, n (%)			
Never smoker	290 (50.9)	84 (43.3)	−0.152
Previous smoker	184 (32.3)	81 (41.8)	0.197
Current smoker	96 (16.8)	29 (14.9)	−0.052
Alcohol consumption, n (%)			
No drinking	92 (29.1)	25 (27.5)	−0.036
Moderate drinking (1 per day)	211 (66.8)	65 (71.4)	0.101
More than moderate drinking (> 1 per day)	13 (4.1)	1 (1.1)	−0.190
BMI, mean (SD)	29.6 (7.1)	31.8 (8.3)	0.290
BMI category, n (%)			0.223
Normal/overweight	335 (58.3)	92 (47.2)	
Obese	240 (41.7)	103 (52.8)	
Work status, n (%)			
Full time	226 (39.5)	35 (18.0)	−0.487
Part time	55 (9.6)	15 (7.7)	−0.067
At home	54 (9.4)	13 (6.7)	−0.101
Student	17 (3.0)	7 (3.6)	0.036
Disabled	92 (16.1)	55 (28.4)	0.298
Retired	128 (22.4)	69 (35.6)	0.293
Insurance, n (%)			
None	3 (0.5)	2 (1.0)	0.058
Private	360 (63.9)	82 (42.9)	−0.430
Medicaid	15 (2.7)	6 (3.1)	0.028
Medicare	185 (32.9)	101 (52.9)	0.412

mCCI was 2.3 (0.6) and the most common comorbidities were diabetes mellitus (42.6%), solid-tumor cancer (21.0%), liver disease (20.5%), and COPD (10.3%; Supplementary Table 2, available with the online version of this article). The distribution of mCCI among this patient population is shown in Supplementary Table 3. The majority of patients in the high mCCI group (153 patients, 78.5%) had 1 comorbid condition in addition to RA (mCCI = 2), while a smaller number of patients had 2 (34 patients, 17.4%), 3 (3 patients, 1.5%), or 4 (5 patients, 2.6%) comorbid conditions in addition to RA.

Study outcomes by comorbidity burden. The unadjusted analysis of changes in disease activity and HAQ at 6 and 12 months is presented in Table 2. Patients in both comorbidity cohorts had improvement from baseline in CDAI and HAQ at 6 and 12 months, with no significant differences between high versus low mCCI. Similar results were observed in the adjusted analyses (Figure 1); variables are included in Figure 1 legend and included baseline disease activity and baseline functional status. Regarding the primary endpoint, the mean change in CDAI at 6 months was

−7.57 for patients with low mCCI and −7.72 for patients with high mCCI. At 12 months, the mean CDAI change was −8.42 for patients with low mCCI and −7.82 for patients with high mCCI ($p > 0.05$).

At 6 months, 75.5% of patients with low mCCI and 74.4% of patients with high mCCI were still receiving TCZ (Supplementary Table 1, available with the online version of this article). Among the 364 patients with low mCCI and 124 patients with high mCCI who received IV TCZ and had available dose information at 6 months, 23.6% and 22.6%, respectively, received 4 mg/kg and 76.4% and 77.4%, respectively, received 8 mg/kg. Of the 34 patients with low mCCI and 6 patients with high mCCI who received SC TCZ and had dose frequency information available at 6 months, 47.1% and 66.7%, respectively, received SC TCZ every 2 weeks and 52.9% and 33.3%, respectively, received SC TCZ every week. At 12 months, 61.4% of patients with a low mCCI and 62.6% of those with a high mCCI were still receiving TCZ. Of the 306 patients with low mCCI and 106 patients with high mCCI receiving

Table 1B. Clinical characteristics at baseline among patients with low versus high comorbidity burden who initiated TCZ.

Characteristic	Low Burden (mCCI < 2), n = 575	High Burden (mCCI ≥ 2), n = 195	Standardized Difference
Treatment history			
Prior no. csDMARD (including current), mean (SD)	2.1 (1.3)	2.4 (1.3)	0.238
Prior biologic use, n (%)			
0	27 (4.7)	6 (3.1)	-0.084
1	127 (22.1)	38 (19.5)	-0.064
2	193 (33.6)	59 (30.3)	-0.071
≥ 3	228 (39.7)	92 (47.2)	0.152
Current concomitant medication, n (%)			
Monotherapy	192 (33.4)	66 (33.8)	0.010
Combination therapy			
MTX	238 (41.4)	67 (34.4)	-0.207
MTX + other csDMARD	98 (17.0)	53 (27.2)	0.333
Other csDMARD	47 (8.2)	9 (4.6)	-0.180
Prednisone use, n (%)			
No use	374 (65.4)	131 (68.2)	0.060
≤ 5 mg	97 (17.0)	34 (17.7)	0.020
> 5 to 7.5 mg	10 (1.7)	5 (2.6)	0.059
> 7.5 to 10 mg	72 (12.6)	16 (8.3)	-0.139
> 10 mg	19 (3.3)	6 (3.1)	-0.011
Prednisone dose, mg, mean (SD)	7.8 (4.7)	7.9 (6.6)	0.006
Disease activity			
CDAI, mean (SD)	23.9 (13.9)	25.7 (13.4)	0.133
Low, n (%)	97 (16.9)	22 (11.3)	-0.161
Moderate, n (%)	181 (31.5)	61 (31.3)	-0.004
High, n (%)	297 (51.7)	112 (57.4)	0.116
HAQ, mean (SD)	0.6 (0.5)	0.7 (0.6)	0.260
Patient-reported fatigue (0–100), mean (SD)	51.3 (28.6)	58.2 (27.6)	0.246
Morning stiffness (yes/no), n (%)	513 (89.8)	171 (89.1)	-0.025
Morning stiffness time, h, mean (SD)	1.7 (3.0)	2.4 (4.7)	0.192

BMI: body mass index; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; mCCI: modified Charlson Comorbidity Index; MTX: methotrexate; RA: rheumatoid arthritis; TCZ: tocilizumab.

IV TCZ with available dose information at 12 months, 16% and 18.9%, respectively, received IV TCZ 4 mg/kg, and 84.0% and 81.1%, respectively, received IV TCZ 8 mg/kg. Of the 25 patients with low mCCI and 7 patients with high mCCI who received SC TCZ and had dose frequency information available at 12 months, 56.0% and 71.4%, respectively, received SC TCZ every 2 weeks, and 44.0% and 28.6%, respectively, received SC TCZ every week. The proportions of patients with an increase in IV dose or SC TCZ frequency at 6 and 12 months are shown in Supplementary Table 1 (available with the online version of this article) and were similar between high and low mCCI.

Patient baseline characteristics by BMI. Of the 805 TCZ initiators, 449 (55.8%) were categorized as nonobese [BMI ≤ 30; mean (SD) BMI, 24.9 (3.1) kg/m²], of whom 31 were underweight (BMI < 18.5), 185 were normal weight (BMI > 18.5 and ≤ 24.9), and 233 were overweight (BMI > 25 and ≤ 29.9). There were 356 patients (44.2%) categorized as obese [BMI > 30; mean (SD) BMI, 36.7 (6.2) kg/m²], of whom 180 were obese class I (BMI > 30 and ≤ 34.9) and 176 were obese class II or III (BMI ≥ 35; Table 3A). A total of 152 obese patients and 2 nonobese

patients weighed ≥ 100 kg at baseline (Supplementary Table 4, available with the online version of this article). As shown in Table 3B, > 95% of patients were biologic experienced, and about one-third of patients received TCZ as monotherapy. Most patients [n = 739 (91.8% of all initiators)] were treated with IV TCZ. Of the IV TCZ initiators, 416 (56.3%) were nonobese and 323 (43.7%) were obese; 428 (57.9%) had available dose information at baseline [nonobese: 231 (55.5%); obese: 197 (61.0%)]. Of the IV TCZ initiators with dose available, 243 (56.8%) received 4 mg/kg [nonobese: 127 (55.0%); obese: 116 (58.9%)] and 185 (43.2%) received 8 mg/kg [nonobese: 104 (45.0%); obese: 81 (41.1%); Supplementary Table 5]. Of the 48 (6.0% of all initiators) patients who initiated SC TCZ, 23 (47.9%) were nonobese and 25 (52.1%) were obese. Of the 48 SC TCZ initiators, 30 (62.5%) had baseline dose frequency available [nonobese: 16 (69.6%); obese: 14 (56.0%)]. Of these, 13 (43.3%) received TCZ every 2 weeks [nonobese: 8 (50.0%); obese: 5 (35.7%)] and 17 (56.7%) received TCZ every week [nonobese: 8 (50.0%); obese: 9 (64.3%)].

Compared with nonobese patients, obese patients were

Table 2. Unadjusted changes in disease activity and HAQ at 6 and 12 months* after initiation of TCZ in patients with low vs high comorbidity burden.

Outcome	Low Burden* (mCCI < 2), n = 575	High Burden* (mCCI ≥ 2), n = 195	Unadjusted Difference or OR†	p
6 months				
Continuous outcome				
Change in CDAI	-7.57 (13.65)	-7.72 (13.62)	-0.15 (-2.37-2.07)	0.897
Change in HAQ	-0.05 (0.41)	-0.09 (0.43)	-0.04 (-0.11-0.30)	0.263
Binary outcome				
Achievement of MCID, CDAI	50.87%	44.62%	0.78 (0.45-1.41)	0.132
Achievement of MCID, HAQ	29.96%	31.79%	1.09 (0.76-1.55)	0.638
Achievement of LDA	24.70%	21.54%	0.84 (0.57-1.24)	0.372
12 months				
Continuous outcome				
Change in CDAI	-8.42 (14.24)	-7.82 (14.52)	0.59 (-1.74-2.92)	0.617
Change in HAQ	-0.05 (0.40)	-0.11 (0.42)	-0.06 (-0.13-0.01)	0.080
Binary outcome				
Achievement of MCID, CDAI	52.28%	49.74%	0.90 (0.65-1.25)	0.541
Achievement of MCID, HAQ	27.09%	30.05%	1.16 (0.81-1.66)	0.429
Achievement of LDA	30.43%	31.28%	1.04 (0.73-1.48)	0.825

* Continuous outcomes expressed as mean (SD); binary outcomes expressed as percent response rate. † Continuous outcomes expressed as β (95% CI); binary outcomes expressed as OR (95% CI). CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; LDA: low disease activity; mCCI: modified Charlson Comorbidity Index; MCID: minimum clinically important difference; TCZ: tocilizumab.

younger [mean (SD) age, 56.7 (12.0) vs 59.0 (13.7) yrs], had a shorter mean (SD) disease duration [11.4 (8.6) vs 12.6 (9.7) yrs], had higher mean (SD) baseline HAQ [0.7 (0.5) vs 0.6 (0.5)] scores, higher mean (SD) mCCI scores [1.4 (0.7) vs 1.3 (0.6)], and worse mean (SD) patient-reported fatigue scores [55.9 (28.3) vs 50.6 (28.5); Table 3A–B]. Baseline mean CDAI was in the high disease activity range in both subgroups but was higher in patients who were obese [mean (SD): 25.4 (14.3) vs 23.6 (13.4)].

Study outcomes by BMI. The unadjusted analyses of changes in disease activity and HAQ at 6 and 12 months are shown in Table 4. Patients in both obesity cohorts had comparable improvement from baseline in CDAI and HAQ at 6 and 12 months. Similar results were noted in adjusted analyses (Figure 2). The variables for which the regression models were adjusted are included in the legend of Figure 2 and included baseline disease activity and baseline functional status. Regarding the primary outcome, the mean change in CDAI at 6 months was -7.77 for nonobese patients and -7.38 for obese patients, and at 12 months was -8.24 for nonobese patients and -8.09 for obese patients ($p > 0.05$). Only HAQ improvement reached statistical significance between the groups at 12 months, in favor of nonobese patients; however, the β coefficient was below the reference MCID for HAQ (0.11).

At 6 months, 76.2% of nonobese patients and 73.3% of obese patients were still receiving TCZ (Supplementary Table 5, available with the online version of this article). Among the 288 nonobese patients and 221 obese patients who received IV TCZ and had available dose information at 6 months, 21.2% and 26.7%, respectively, received 4 mg/kg, and 78.8% and 73.3%, respectively, received 8 mg/kg. Of the 23 nonobese patients and 18 obese patients who received SC TCZ and had dose frequency

information available at 6 months, 56.5% and 38.9%, respectively, received SC TCZ every 2 weeks and 43.5% and 61.1%, respectively, received SC TCZ every week. At 12 months, 63.9% of nonobese patients and 58.1% of obese patients were still receiving TCZ. Of the 245 nonobese patients and 184 obese patients receiving IV TCZ with available dose information at 12 months, 15.9% and 17.4%, respectively, received IV TCZ 4 mg/kg and 84.1% and 82.6% received IV TCZ 8 mg/kg. Of the 26 nonobese patients and 7 obese patients who received SC TCZ and had dose frequency information available at 12 months, 57.7% and 57.1%, respectively, received SC TCZ every 2 weeks and 42.3% and 42.9%, respectively, received SC TCZ every week. The proportions of patients with an increase in IV TCZ dose or SC TCZ frequency at 6 and 12 months are shown in Supplementary Table 5 and were similar for obese and nonobese patients.

DISCUSSION

The high prevalence of comorbidities^{1,21} and of obesity⁷ in patients with RA and the association between comorbidity and RA disease progression²² have led to extensive investigation into the potential effect of comorbid conditions and of obesity on disease-modifying antirheumatic drug (DMARD) efficacy. Patients with a higher comorbidity burden may be less likely to start a biologic agent early in their disease course²¹. Obesity has also been associated with poorer clinical outcomes in patients with RA, despite DMARD therapy, and efficacy of tumor necrosis factor inhibitors is negatively affected by patients' weight^{10,12,13,16,23,24,25}. The effect of TCZ in patients with higher comorbidity burden has not previously been evaluated in patients with RA. Also, few real-world studies have investigated the effectiveness of TCZ in obese patients^{26,27}. Using data from the largest US-based RA registry, we demonstrated that patients

Figure 1. Adjusted changes in disease activity and HAQ at 6 and 12 months* after initiation of TCZ in patients with high (mCCI ≥ 2) versus low (mCCI < 2) comorbidity burden. * The 6-month visit occurred in a window of 4–8 months; the 12-month visit occurred in a window of 10–14 months. [†] A β coefficient < 0 indicates that, on average, patients with high comorbidity burden show a greater level of improvement in the outcome when compared to those with low disease burden, after adjustment for covariates. Additionally, an OR > 1 indicates that patients with high comorbidity burden have higher odds of achieving the outcome compared to those with low disease burden, after adjustment for covariates. Adjustment covariates: age, duration of RA, race, college education, smoking status, alcohol consumption, BMI, work status, insurance type, number of prior csDMARD, current csDMARD use, number of prior biologics used, current prednisone use, CDAI at initiation, HAQ at initiation, patient-reported fatigue at initiation, and duration of morning stiffness at initiation. [‡] CDAI ≤ 10 at baseline, MCID = 2; CDAI > 10 to ≤ 22 at baseline, MCID = 6; CDAI > 22 at baseline, MCID = 11. [§] MCID = 0.22. ^{||} LDA, CDAI ≤ 10 . BMI: body mass index; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; LDA: low disease activity; mCCI: modified Charlson Comorbidity Index; MCID: minimum clinically important difference; RA: rheumatoid arthritis; TCZ: tocilizumab.

who initiated TCZ improved in CDAI and HAQ at 6 and 12 months, with similar improvements in patients with high and low comorbidity burden and obese and nonobese patients.

The current study provides insight into TCZ use in real-life practice in the United States. We found TCZ is frequently used in patients with comorbidities and obesity, as 25% of TCZ initiators in our study had a high mCCI and 45% were categorized as obese. More than 95% of the patients included in our analysis had failed other biologics prior to TCZ initiation. The vast majority of patients received IV TCZ, and most patients were treated with IV TCZ 8 mg/kg at 6 months post-initiation. Patients in the Corrona registry are not mandated to receive

a specific therapeutic regimen. Instead, treatment decisions related to the choice of medication as well as changes in dosage and frequency rely on the physician's discretion. The fact that IV TCZ is administered on a mg/kg basis may have allowed rheumatologists to more easily tailor TCZ dose based on patients' weight or lack of response to the recommended initial dosing of 4 mg/kg every 4 weeks (increasing to 8 mg/kg based on clinical response). Thus, the dose flexibility of TCZ may have improved disease control in patients who would have been nonresponders if treated with a biologic not adjusted for body weight.

The major strength of this study was the use of a large US database collecting real-world data on clinical response in

Table 3A. Patient demographics at baseline in nonobese versus obese patients who initiated TCZ.

Characteristic	Nonobese (BMI < 30), n = 449	Obese (BMI ≥ 30), n = 356	Standardized Difference
Female, n (%)	363 (80.8)	282 (79.2)	−0.041
Age, yrs, mean (SD)	59.0 (13.7)	56.7 (12.0)	−0.182
Duration of RA, yrs, mean (SD)	12.6 (9.7)	11.4 (8.6)	−0.129
Race, n (%)			
White	404 (90.0)	319 (89.6)	−0.012
Black/African American	16 (3.6)	21 (5.9)	0.11
Asian	16 (3.6)	1 (0.3)	−0.241
Other	13 (2.9)	15 (4.2)	0.071
Education (college or above), n (%)	277 (61.8)	211 (59.8)	−0.042
Smoking status, n (%)			
Never smoker	211 (47.2)	184 (52.3)	0.102
Previous smoker	158 (35.3)	117 (33.2)	−0.044
Current smoker	78 (17.4)	51 (14.5)	−0.081
Alcohol consumption, n (%)			
No drinking	65 (26.9)	57 (30.8)	0.087
Moderate drinking (1 per day)	168 (69.4)	122 (65.9)	−0.074
More than moderate drinking (> 1 per day)	9 (3.7)	6 (3.2)	−0.026
Work status, n (%)			
Full time	145 (32.5)	127 (35.8)	0.069
Part time	44 (9.9)	29 (8.2)	−0.059
At home	37 (8.3)	33 (9.3)	0.035
Student	19 (4.3)	5 (1.4)	−0.172
Disabled	80 (17.9)	77 (21.7)	0.094
Retired	121 (27.1)	84 (23.7)	−0.08
Insurance, n (%)			
None	4 (0.9)	1 (0.3)	−0.08
Private	254 (57.6)	206 (59.4)	0.036
Medicaid	8 (1.8)	14 (4.0)	0.132
Medicare	175 (39.7)	126 (36.3)	−0.069
BMI category			
Underweight (BMI < 18.5)	31 (3.9)	–	
Normal weight (BMI > 18.5 and ≤ 24.9)	185 (23.0)	–	
Overweight (BMI > 25 and ≤ 29.9)	233 (28.9)	–	
Obese class I (BMI > 30 and ≤ 34.9)	–	180 (22.4)	
Obese class II & III (BMI ≥ 35)	–	176 (21.9)	
Comorbidity burden*			
CCI, mean (SD)	1.3 (0.6)	1.4 (0.7)	0.153
Low (1), n (%)	335 (78.5)	240 (70.0)	−0.195
High (≥ 2), n (%)	92 (21.5)	103 (30.0)	0.195
History of diabetes mellitus, n (%)	25 (5.6)	58 (16.3)	0.348

patients, along with BMI and comorbid conditions. Although previously published studies investigating TCZ in obese patients with RA have similarly shown no difference in clinical response compared to nonobese patients^{26,27}, a recent report showed impaired improvement in 28-joint count Disease Activity Score in women with RA treated with TCZ²⁸. Our present study expands upon previous findings to present data from patients in the United States and to describe changes in CDAI and HAQ in a larger sample of patients.

There are several notable points to consider in the interpretation of our findings. The distribution of mCCI indicates that the majority of patients in this analysis with mCCI ≥ 2 had 1–2 comorbidities plus RA. TCZ effectiveness was not separately analyzed for patients with > 2 comorbidities, and the relationship between specific comorbidities on TCZ efficacy was not examined. The

effectiveness of TCZ in patients with extreme obesity or with weight > 100 kg, populations who would be more likely to receive the maximum dose of TCZ (162 mg weekly for SC TCZ and 800 mg/kg every 4 weeks for IV TCZ), was not separately examined. Thus, these results should be interpreted with caution for patients with multiple comorbidities or extreme obesity. The mCCI does not include all comorbidities in patients with RA (e.g., interstitial lung disease), and it is possible some patients in the low comorbidity burden group may have had a comorbidity that was not recorded by the mCCI; however, the CCI has been extensively validated and has shown strong correlation with other comorbidity indices in patients with RA²⁹. Baseline TCZ dose information was available for only about 57% of patients, resulting in an insufficient sample size for meaningful comparison of TCZ effectiveness stratified by dose in low versus

Table 3B. Clinical characteristics at baseline in nonobese vs obese patients who initiated TCZ.

Characteristic	Nonobese (BMI < 30), n = 449	Obese (BMI ≥ 30), n = 356	Standardized Difference
Treatment history			
Prior no. csDMARD (including current), mean (SD)	2.2 (1.3)	2.1 (1.3)	−0.103
Prior biologic use, n (%)			
0	18 (4.0)	15 (4.2)	0.01
1	103 (22.9)	69 (19.4)	−0.087
2	135 (30.1)	125 (35.1)	0.108
≥ 3	193 (43.0)	147 (41.3)	−0.034
Current concomitant medication, n (%)			
Monotherapy	157 (35.0)	108 (30.3)	−0.099
Combination therapy			
MTX	180 (40.1)	148 (41.6)	−0.04
MTX + other csDMARD	69 (15.4)	82 (23.0)	0.21
Other csDMARD	43 (9.6)	18 (5.1)	−0.24
Prednisone use, n (%)			
None	293 (65.8)	234 (66.1)	0.005
≤ 5 mg	76 (17.1)	59 (16.7)	−0.011
> 5 to 7.5 mg	6 (1.3)	9 (2.5)	0.087
> 7.5 to 10 mg	56 (12.6)	39 (11.0)	−0.049
> 10 mg	14 (3.1)	13 (3.7)	0.029
Prednisone dose, mg, mean (SD)	7.7 (4.9)	8.1 (5.5)	0.075
Disease activity			
CDAI, mean (SD)	23.6 (13.4)	25.4 (14.3)	0.125
Low, n (%)	69 (15.4)	56 (15.7)	0.01
Moderate, n (%)	150 (33.4)	103 (28.9)	−0.097
High, n (%)	230 (51.2)	197 (55.3)	0.082
HAQ, mean (SD)	0.6 (0.5)	0.7 (0.5)	0.153
Patient-reported fatigue (0–100), mean (SD)	50.6 (28.5)	55.9 (28.3)	0.187
Morning stiffness (yes/no), n (%)	399 (89.9)	315 (89.5)	−0.012
Morning stiffness time, h, mean (SD)	1.8 (3.3)	1.9 (3.6)	0.012

* The prevalence of other comorbidities recorded by Corrona at drug initiation was low and comparable between the BMI cohorts. BMI: body mass index; CCI: Charlson Comorbidity Index; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; MTX: methotrexate; RA: rheumatoid arthritis; TCZ: tocilizumab.

high comorbidity burden or in nonobese versus obese groups. Because most patients received IV TCZ, our results may not be generalizable to SC use. The sample size of patients receiving SC TCZ was not sufficient to generate meaningful results in a separate analysis — only 47 of the 770 TCZ initiators included in the analysis of comorbidity burden and 48 of the 805 TCZ initiators included in the analysis of obesity initiated SC TCZ. However, clinical studies have demonstrated no difference in the efficacy of SC TCZ compared with IV TCZ for improving disease activity in patients with RA^{30,31}. Thus, our results may provide relevant information for patients treated with SC TCZ. Regarding the missing dose information on the robustness of our results, our study was not undertaken to establish the effectiveness of a specific TCZ dose in the setting of obesity or comorbidities. While the dose information data are incomplete, they still reflect the actual use of TCZ in the registry. The percentage of missing data by TCZ dose was not different by obesity or comorbidity status. The distribution of IV TCZ 4 versus 8 mg/kg dose at baseline is also balanced between the cohorts, and

similar patterns are noted for the percentage of patients who increase their IV TCZ dose from 4 to 8 mg/kg at 6 and 12 months. Therefore, the lack of dosing data was not believed to preferentially skew the results in favor of patients with high or low comorbidities or BMI. The overwhelming use of IV TCZ in the United States is 8 mg/kg, and because 93.8% of the patients were receiving IV TCZ in our study, these findings appear representative of patients receiving TCZ in real-world situations.

This analysis demonstrates that TCZ is used frequently in real-world practice in patients with RA with comorbid conditions or obesity and was effective regardless of comorbidity burden or obesity.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

Table 4. Unadjusted changes in disease activity and HAQ at 6 and 12 months* after initiation of TCZ in nonobese versus obese patients.

Outcome	Nonobese* (BMI < 30), n = 449	Obese* (BMI ≥ 30), n = 356	Unadjusted Difference or OR†	p
6 months				
Continuous outcome				
Change in CDAI	-7.77 (13.12)	-7.38 (14.05)	0.39 (-1.49 to 2.28)	0.682
Change in HAQ	-0.06 (0.41)	-0.05 (0.42)	0.003 (-0.06 to 0.06)	0.928
Binary outcome				
Achievement of MCID, CDAI	51.01%	46.48%	0.84 (0.60–1.17)	0.203
Achievement of MCID, HAQ	30.32%	30.17%	0.87 (0.59–1.28)	0.965
Achievement of LDA	26.95%	19.66%	0.70 (0.48–1.01)	0.016
12 months				
Continuous outcome				
Change in CDAI	-8.24 (13.39)	-8.09 (15.27)	0.15 (-1.84 to 2.14)	0.880
Change in HAQ	-0.07 (0.40)	-0.04 (0.42)	0.03 (-0.02 to 0.09)	0.255
Binary outcome				
Achievement of MCID, CDAI	53.14%	49.15%	0.85 (0.64–1.13)	0.263
Achievement of MCID, HAQ	27.50%	27.67%	1.00 (0.53–1.21)	0.959
Achievement of LDA	32.07%	27.53%	0.80 (0.59–1.09)	0.163

* Continuous outcomes expressed as mean (SD); binary outcomes expressed as percent response rate. † Continuous outcomes expressed as β (95% CI); binary outcomes expressed as OR (95% CI). BMI: body mass index; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; LDA: low disease activity; MCID: minimum clinically important difference; TCZ: tocilizumab.

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Figure 2. Adjusted changes in disease activity and HAQ at 6 and 12 months* after initiation of TCZ in obese (BMI ≥ 30) versus nonobese (BMI < 30) patients. * The 6-month visit occurred in a window of 4–8 months; the 12-month visit occurred in a window of 10–14 months. [†] A β coefficient < 0 indicates that, on average, obese patients show a greater level of improvement in the outcome when compared to nonobese patients, after adjustment for covariates. Additionally, an OR > 1 indicates that obese patients have higher odds of achieving the outcome compared to nonobese patients, after adjustment for covariates. Adjustment covariates: age, duration of RA, race, college education, smoking status, alcohol consumption, BMI, work status, insurance type, number of prior csDMARD, current csDMARD use, number of prior biologics used, current prednisone use, CDAI at initiation, HAQ at initiation, patient-reported fatigue at initiation, and duration of morning stiffness at initiation. [‡] CDAI ≤ 10 at baseline, MCID = 2; CDAI > 10 to ≤ 22 at baseline, MCID = 6; CDAI > 22 at baseline, MCID = 11. [§] MCID = 0.22. ^{||} LDA, CDAI ≤ 10 . BMI: body mass index; CDAI: Clinical Disease Activity Index; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; LDA: low disease activity; MCID: minimum clinically important difference; RA: rheumatoid arthritis; TCZ: tocilizumab.

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