Impact of anti-rheumatic treatment on the individual components of the ACR composite score in patients with rheumatoid arthritis: real-world data

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Abstract

Objective

Standard criteria for measuring treatment efficacy in patients with rheumatoid arthritis (RA) include American College of Rheumatology (ACR) response rates, which require meeting a threshold of ≥20/50/70% improvement in several physician- and patient-reported measures. We aimed to evaluate the impact of csDMARDs, TNF inhibitors (TNFi), and tofacitinib (TOFA) on ACR components in real-life practice.

Methods

Clinical data of RA patients with a CDAI >10 at the time they started a treatment were pooled from two registries: Ontario Best Practices Research Initiative (OBRI) and RHUMADATA. Endpoints included proportions of patients achieving: ACR20/50/70 responses, ≥20/50/70% improvements and mean percentage improvement in individual ACR components at Month 6. We also adjusted for potential confounders to compare impact of these medications on outcomes of interest.

Results

A total of 669 patients were included (csDMARD, n=157, TNFi, n=252; TOFA, n=260). An overall higher proportion in all three-medication groups achieved ≥20/50/70% improvement in primary ACR components vs. secondary components. Among secondary components, ≥20/50/70% improvement rates were numerically highest for PhGA and lowest for HAQ-DI and pain. Among ACR20/50/70 responders for all medications, the mean percentage improvement was more than 80% for primary components, and ranged from 30% to 80% for secondary components. A significantly lower proportion of patients in TNFi group achieved to at least 50% improvement in pain compared to TOFA after adjusting.

Conclusion

In this real-world practice, physician-reported measures contribute slightly more to overall ACR20/50/70 responses. Pain was the most important factor in achieving an ACR50 TOFA users, possibly reflecting the different effects of JAKi on pain.

Key words

rheumatoid arthritis, response, treatment, ACR20/50/70, real-world data

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Significance and innovation

- *Swollen and tender joints as primary components of ACR20/50/70 are improving more than secondary components (PhGA, PtGA, HAQ_DI, Pain, CRP) regardless of type of anti-rheumatic therapy.*
- *Physician reported measures (PhGA, swollen and tender joints) are improving more than patient reported outcomes (PtGA, HAQ-DI, Pain) regardless of type of anti-rheumatic therapy.*
- *In TOFA users, the most important factor in achieving an ACR50 TOFA users, possibly reflecting the different effects of JAKi on pain.*

Competing interests: see page 1828.

Introduction

The American College of Rheumatology (ACR) response criteria, one of the common outcome measures in rheumatoid arthritis (RA), require meeting a threshold of ≥20/50/70% improvement (ACR20/50/70, respectively) in both tender and swollen joint counts (TJC and SJC, respectively; primary criteria) and at least 3 of 5 secondary criteria: physician global assessment (PhGA), patient global assessment of disease activity (PtGA), patient-reported pain (Pain), Health Assessment Questionnaire-Disability Index (HAQ-DI), and C-reactive protein (CRP). Although ACR response results are not usually calculated in clinical practice, many rheumatologists will gather all ACR response components individually (1). Recent guidelines on management of RA have highlighted the role of patient global care and shifting from older drugs (*e.g.* steroids) to newer drugs such as Janus kinase inhibitors (JAKi) (2).

TNF inhibitors (TNFi) has been available as a therapeutic option for RA patients for over 20 years, and its efficacy has been demonstrated in several RCTs and real-life studies (3-5). JAKi are alternative to biologic disease-modifying anti-rheumatic drugs (bDMARDs) and is prescribed alone or with MTX. Tofacitinib (TOFA) was the first JAKi approved on June 2014 in Canada at a dose of 5 mg twice daily to treat adults with moderately to severely active rheumatoid arthritis (RA disease) usually after inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate (MTX). The comparative efficacy of JAKi and TNFi has been evaluated in a few RCTs (6, 7). The impact of TOFA has also been investigated on ACR20/50/70 (8) or ACR20/50/70 components (9) in randomised clinical trials (RCT) including long-term extension RCT. However, there are not many observational cohort studies that investigated efficacy of TOFA on ACR20/50/70 response criteria and compared the improvement rates in individual ACR components between a JAKi, a TNFi and a csDMARD. Reed *et al*. 2019 conducted an observational study to examine the TNFi and TOFA efficacy using LDA/remission and ACR20 improvement as outcomes (10). They found similar efficacy between TOFA alone and TOFA in combination with MTX. Similar results were found in recent studies conducted by RHUMADATA (unpublished observation) and OBRI (unpublished observation) in Canada, by comparing drug discontinuation due to any reason between TOFA with MTX *versus* TOFA alone treatment groups. We aimed to determine the impact of TOFA, TNFi (with or without csDMARDs)) in comparison with csDMARDs alone on ACR components improvement in an observational study of RA.

Methods

Data sources

The OBRI is a multicentre registry across Ontario, Canada, collecting data from rheumatologists and RA patients at enrolment and follow-up. It incorporates rheumatologist assessments from approximately one-third of the rheumatologists in the province of Ontario. Patients are eligible to be enrolled if they are ≥16 years of age at the time of diagnosis, ≥18 years of age at enrolment, have a rheumatologist confirmed RA diagnosis, and have at least one swollen joint. Enrolled patients are interviewed every 6 months by phone and seen by their rheumatologist in routine care. At enrolment, patients are asked for their general medical history including comorbidity status. Rheumatologists are also expected to report any history of previous comorbidity including cardiovascular disease (CVD), and RA disease activity including inflammatory markers, patient global, physician global, tender and swollen joint counts. Data on socio-demographics, smoking status, height, weight, and any prior and current medications are recorded during the rheumatologist enrolment visit or the patient's interview. Patient-reported outcomes for functional status are also collected. At follow-up visits, all the information mentioned above is updated. RA medication changes (including discontinuation and reasons for discontinuation) between visits are also captured. Rheumatologists report any

incident of comorbidity and re-assess disease activity during every follow-up visit.

The RHUMADATA clinical database and registry monitors the clinical care of all the patients with inflammatory diseases seen at the *Institut de Rhumatologie de Montréal* (IRM), the *Centre de l'ostéoporose et de rhumatologie de Québec* (CORQ), and the Clinique de santé Jacques-Cartier (CSJC), the largest rheumatologic clinics in the province of Québec, Canada. RHUMADATA™ has been collecting real-world observational data since 1998 from all the patients and all the visits with a given diagnosis. The database currently includes the treatment history of more than 6000 patients with inflammatory disease (rheumatoid arthritis (RA), ankylosing spondylitis (AS), spondyloarthritis (SPA)). Data collected at all visits includes: demographics, disease history, laboratory values (Rheumatoid factor (RF), anti-circulated protein antibody (ACPA), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), all disease activity scores (disease activity score (DAS) CRP and ESR, Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI)), patient-reported outcomes (PROs) including health assessment questionnaire disability index (HAQ-DI), morning stiffness, patient global evaluation of disease activity, patient evaluation of pain, and physician global evaluation of disease activity. Comorbidities including, but not limited to, cardiovascular disease, diabetes, high blood pressure, cancer, and infections are also collected. Medication usage information for disease control is entered into the database (start and termination data as well a reason for termination).

Institutional ethics approval was obtained for both OBRI (University Health Network research ethics board no. 07-0729 AE) and RHUMADATA™ (Institutional Review Board Services no. IRB00005290), and all patients provided informed consent before study enrolment.

This study was conducted in compliance with the principles of the Declaration of Helsinki.

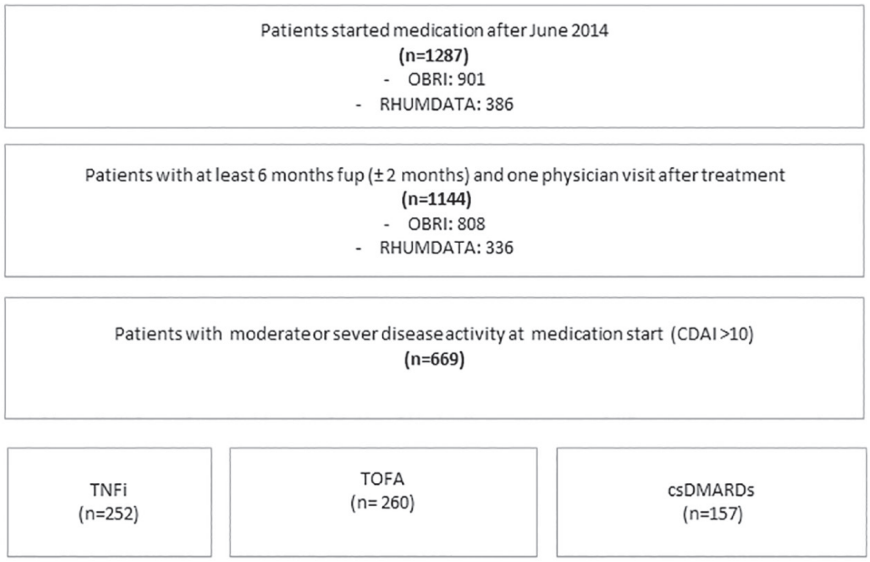

Fig. 1. Cohort flowchart.

Study population and data collection

RA active patients (≥1 swollen joint) who initiated csDMARDs (as mono or combination therapy), TOFA (with or without csDMARDs), TNFi (with or without csDMARDs) and are on treatment for at least three months between 1st June 2014 (TOFA approval date in Canada) and 31st December 2020. Patients must have at least 1 visit during follow-up. Patients must also have all ACR measured components available both at baseline (defined as treatment initiation) and 6 months follow-up (±60 days' window). In the event of more than one visit within this timeframe, the closest to 6 months was used. Patients were excluded if they were in low disease activity (LDA) (CDAI <10) or remission state (CDAI <2.8) at baseline using CDAI composite score.

Treatment groups

Treatment groups included TOFA (with or without csDMARDs), TNFi (with or without csDMARDs), and csDMARDs (MTX, LEF, HCQ, SSZ) as monotherapy or combination therapy.

Outcomes

The following clinical RA measures assessed by rheumatologists are recorded as routine care: SJC28, TJC28, PtGA, PhGA, pain, HAQ-DI, CRP, ESR, Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI).

- *Primary outcomes*

- Proportion achieving overall ACR20/50/70 responses (response rates) at month 6.
- Proportion of patients achieving ≥20/50/70% improvement from baseline on each ACR components (improvement rates; TJC28, SJC28, PhGA, PtGA, Pain, HAQ-DI, and CRP) at month 6.

- *Secondary outcomes*

- Mean percentage improvement in ACR components, CDAI and SDAI in patients who achieved an ACR20/50/70 response at month 6.
- Proportion of patients in remission (CDAI <2.8, SDAI <3.3) and low disease activity (CDAI <10, SDAI <11), measured by CDAI and SDAI, in those achieving ACR20/50/70 response at month 6.

Statistical analysis

Baseline characteristics were described using the mean and standard deviation (SD) or median (Inter quartile range) for continuous variables or the count and proportion for categorical variables. ACR 20/50/70 response achievement at 6 months in different treatment were presented using tables and figures including bar charts. Patients who switched their treatment between 3 and 6 months were considered as non-responders for binary outcomes and for the continuous variable the last disease

Table I. Baseline characteristics of included patients.

Variables	Type of treatment				
	Total (n=669)	csDMARDs α (n=157)	TNFi £ (n=252)	TOFA© (n=260)	*p*-value
Gender					α vs. £ (0.2117) α vs. © (0.4838) £ vs. © (0.0255)
Female (%)	458 (68.5)	106 (67.5)	185 (73.4)	167 (64.2)	
Age (years) at initiation of treatment					
n	668	156	252	260	
Mean ± SD	57.47 ± 13.57	56.35 ± 14.39	56.98± 13.61	58.62 ± 12.99	α *vs*. £ (0.6468) α *vs*. © (0.0992) £ *vs*. © (0.1733)
Education status					
n	634	143	240	251	
Post-secondary (%)	400 (63.1)	97 (67.8)	146 (60.8)	157 (62.5)	α *vs*. £ (0.1706) α *vs*. © (0.2969) £ *vs*. © (0.6940)
Smoking status					
n	608	145	231	232	
Current smoker	92 (15.1)	23 (15.8)	35 (15.1)	34 (14.6)	α *vs*. £ (0.8520) α *vs*. © (0.7511) £ *vs*. © (0.8819)
Disease duration (years) at initiation of treatment					
n	669	157	252	260	
Mean ± SD	7.54 ± 9.03	2.97 ± 7.39	7.42 ± 8.30	10.40 ± 9.48	α *vs*. £ (<0.0001) α *vs*. © (<0.0001) £ *vs*. © (<0.0001)
Positive rheumatoid factor					
n	631	152	232	247	
Positive (%)	456 (72.2)	111 (73.0)	174 (75.0)	171 (69.2)	α *vs*. £ (0.6731) α *vs*. © (0.4115) £ *vs*. © (0.1595)
Positive anti-cyclic citrullinated protein antibody					
n	438	114	161	163	
Positive (%)	284 (64.8)	75 (65.8)	106 (65.8)	103 (63.2)	α *vs*. £ (0.9933) α *vs*. © (0.6569) £ *vs*. © (0.6190)
Erythrocyte Sedimentation Rate (mm/hr)					
n	609	144	232	233	
Mean ± SD	22.7 ± 18.2	26.2 ± 18.0	21.9± 16.6	21.4 ± 19.6	α *vs*. £ (0.0261) α *vs*. © (0.0141) £ *vs*. © (0.7935)
C-reactive Protein (mg/L)					
n	637	150	238	249	
Mean ± SD	12.0 ± 17.2	13.7 ± 18.3	12.1 ± 18.0	10.8 ± 15.6	α *vs*. £ (0.3798) α *vs*. © (0.0979) £ *vs*. © (0.3797)
Patient global assessment					
n	664	153	252	259	
Mean ± SD	5.56± 2.47	5.69 ± 2.52	5.45 ± 2.48	5.58 ± 2.44	α *vs*. £ (0.3381) α *vs*. © (0.6456) £ *vs*. © (0.5619)
Physician global assessment					
n	641	143	241	257	
Mean ± SD	5.23 ± 1.99	5.28 ± 2.19	5.16 ± 2.04	5.28 ± 1.83	α *vs*. £ (0.5981) α *vs*. © (0.9933) £ *vs*. © (0.5285)
Swollen joint counts					
n	669	157	252	260	
Mean ± SD	7.20± 4.23	7.03 ± 4.49	7.05 ± 3.86	7.45 ± 4.40	α *vs*. £ (0.9537) α *vs*. © (0.3267) £ *vs*. © (0.2916)
Tender joint counts					
n	669	157	252	260	
Mean ± SD	7.47 ± 5.87	8.27 ± 5.64	7.47 ± 5.80	7.00 ± 6.05	α *vs*. £ (0.1804) α *vs*. © (0.0320) £ *vs*. © (0.3607)

Variables	Type of treatment				
	Total (n=669)	csDMARDs α (n=157)	TNFi £ (n=252)	TOFA© (n=260)	*p*-value
Clinical Disease Activity Index					
n	669	157	252	260	
Mean ± SD	25.6± 10.4	26.4 ± 11.4	25.3 ± 9.97	25.5 ± 10.2	α *vs*. £ (0.3096) α *vs*. © (0.4118) £ *vs*. © (0.8176)
Health Assessment Questionnaire Disability Index					
n	621	130	238	253	
Mean ± SD	1.23 ± 0.72	1.11± 0.74	1.23 ± 0.72	1.28 ± 0.70	α *vs*. £ (0.1202) α *vs*. © (0.0301) £ *vs*. © (0.4728)
Pain					
N	621	130	238	253	
Mean ± SD	5.14 ± 2.71	4.95 ± 2.54	5.10 ± 2.80	5.29 ± 2.70	α *vs*. £ (0.6194) α *vs*. © (0.2449) £ *vs*. © (0.4294)
Previous bDMARD use					
Yes (%)	117 (17.5)	0 (0.0)	12 (4.8)	105 (40.4)	α *vs*. £ (0.1605) α *vs*. © (<0.0001) £ *vs*. © (<0.0001)
Combination with csDMARDs					
Combo therapy (%)	362 (54.1)	72 (45.9)	130 (51.6)	160 (61.5)	α *vs*. £ (<0.0001) α *vs*. © (<0.0001) £ *vs*. © (0.0099)
Use of MTX					
Yes (%)	436 (65.2)	130 (82.8)	154 (61.1)	152 (58.5)	α *vs*. £ (<0.0001) α *vs*. © (<0.0001) £ *vs*. © (0.5214)
Concomitant use of steroids					
Yes (%)	136 (20.3)	20 (12.7)	42 (16.7)	74 (28.5)	α *vs*. £ (0.3318) α *vs*. © (0.0001) £ *vs*. © (0.0001)

activity status before switch was used for assessment at 6 months. For patients who stopped their treatment between 3 and 6 months and did not start any anti-rheumatic medication, their disease activity at 6 months was considered. In addition, we used the area under the receiver operating characteristics curve (ROC AUC) to assess the contribution of each non-mandatory (secondary) ACR component (PhGA, PtGA, Pain, HAQ-DI, and CRP) to the attainment of the overall ACR20/50/70 response rate stratified by three treatment groups through the 6-month follow-up after therapy initiation.

- Advanced analysis

For primary outcomes, we also conducted advanced analyses to adjust for potential confounders (*a priori* list including age, sex, education, smoking status, disease duration, RF presence, and concurrent steroid use). We used a random effect logistic regression model to deal with repeated measures and observation dependency in our longitudinal data. The results were shown as odds ratio (ORs) with 95% confidence interval (95%CI) choosing the TOFA group as reference.

- Sensitivity analysis

We repeated the descriptive analysis for patients with no prior exposure to bDMARDs to check consistency of results.

Results

A total of 669 patients were included (csDMARD, n=157, TNFi, n=252; TOFA, n=260). At baseline, patients starting TOFA had significantly longer disease duration compared to both TNFi and csDMARDs ($p<0.0001$), lower ESR compared to csDMARDs ($p=0.0111$) higher HAQ-DI compared to csDMARDs ($p=0.0301$), failed more bDMARDs compared to both csDMARDs and TNFi ($p<0.0001$) and used more corticosteroids than csDMARDs and TNFi ($p=0.0001$). The MTX use as mono or combo therapy was significantly higher in the csDMARD group compared to the TNFi and TOFA group ($p<0.0001$). The CDAI was similar between the 3 groups (Table I).

ACR20/50/70 response rates and ≥20/50/70% improvement rate in ACR components

ACR 20/50 response rates were numerically lower for the TOFA group compared with csDMARDs and TNFi treated patients, and the ACR70 response was similar in the 3 groups (Table II). Most primary and secondary components across treatment groups surpassed the overall ACR20/50/70 responses rates. An overall higher proportion of patients in all three-medication groups achieved ≥20/50/70% improvement in primary ACR components *versus* secondary components. The improvement in the SJC and TJC were numerically similar between all groups (Table II). Among secondary components, ≥20/50/70% improvement rates were numerically highest for PhGA and lowest for HAQ-DI. In general, ≥20/50/70% improvement rate for physician reported components (SJC,

Table II. Percentage of patients treated with csDMARD, TNFi, and TOFA who reported an a) ACR20 response and ≥20% improvement, and b) ACR50 response and ≥50% improvement, and c) ACR70 response and ≥70% improvement.

	csDMARD (n=157)	TNFi (n=252)	TOFA (n=260)
a) ACR20 response and ≥20% improvement in each component of the ACR20 score, n (%)			
ACR20 response	53.6%	42.0%	28.6%
TJC	72.4%	71.4%	73.0%
SJC	74.3%	78.5%	77.3%
PhGA	77.3%	68.1%	63.5%
PtGA	67.4%	55.3%	46.8%
Pain	43.1%	41.9%	44.5%
HAQ-DI	39.6%	33.5%	31.3%
CRP	53.3%	55.2%	48.0%
b) ACR50 response and ≥50% improvement in each component of the ACR50 score, n (%)			
ACR50 response	27.4%	25.3%	19.4%
TJC	62.1%	63.8%	68.5%
SJC	64.9%	67.8%	67.2%
PhGA	58.3%	51.7%	50.3%
PtGA	44.9%	38.8%	32.7%
Pain	27.6%	23.7%	26.7%
HAQ-DI	23.6%	17.3%	17.7%
CRP	40.9%	41.4%	35.6%
c) ACR70 response and ≥70% improvement in each component of the ACR70 score, n (%)			
ACR70 response	9.5%	8.7%	8.5%
TJC	44.1%	53.3%	53.9%
SJC	49.3%	51.4%	53.0%
PhGA	35.6%	31.4%	28.4%
PtGA	31.9%	18.3%	22.9%
Pain	18.1%	13.6%	13.1%
HAQ-DI	14.2%	10.7%	10.9%
CRP	24.8%	27.6%	22.3%

Analysis is based on observed case data (without imputation) of patients with all 7 components assessed. ACR20/50/70: American College of Rheumatology ≥20/ 50/70% response rates; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; Pain: patient-reported pain (visual analogue scale); PhGA: physician global assessment; PtGA: patient global assessment of disease activity; SJC: swollen joint count; TJC: tender joint count; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; TNFi: tumour necrosis factor inhibitors; TOFA: tofacitinib.

TJC, and PhGA) were higher than patient reported components (PtGA, Pain, and HAQ-DI) across treatment classes (Table II). The rate of improvement ≥20/50/70% in the secondary components of the ACR showed slight variations between treatment groups, but the overall rates of improvement observed were relatively similar between the 3 groups for PhGA, PtGA, HAQ-DI, pain and CRP.

The mean percentage improvement in ACR components and CDAI/SDAI scores in ACR20/50/70 responders

Among ACR20/50/70 responders for all medications, mean percentage improvement was more than 80% for primary components and ranged from 30% to 80% for secondary components (Fig. 2). Compared with ACR20 responders, greater improvement was seen in primary components and secondary components (except CRP) in ACR50/70 responders. Interestingly, the difference between the % improvement in TJC and SJC between ACR20 responders and ACR50/70 responders is about 10%. In other words, the difference is really in the outcomes reported by the patients. The mean percentage improvement for HAQ-DI and pain in ACR20/50/70 responders was higher in the TOFA group compared with the TNFi and csDMARD group. The mean percentage improvement for PtGA was lower for TOFA in ACR20/50/70 responders. Interestingly, the difference between PhGA and PtGA decreases for ACR50/70 responders. The mean percentage improvement in CDAI and SDAI (ranged 72.1–91.7%) was numerically similar between all groups (Fig. 2c). They were also almost similar to the mean percentage improvement of primary components (tender and swollen joint counts). The mean percentage improvement in CDAI and SDAI surpassed 70 % in ACR20 responders.

The CDAI/SDAI LDA and remission rate in ACR20/50/70 responders

Figure 3 shows the proportion of LDA and remission measured by CDAI and SDAI at month 6 among ACR20/50/70 responders. Response rates were similar for CDAI and SDAI. In most cases, the proportion of LDA status based on CDAI or SDAI was slightly lower in the csDMARD group compared to other treatment classes. Generally, the proportion of remission and LDA was higher in patients who achieved ACR70 compared to those achieved ACR50 or ACR20. An ACR70 achievement was not equivalent to remission particularly for the csDMARD and TOFA treatment group. More than 40% and 60% of ACR70 responders in the TOFA and TNFi group, respectively, achieved CDAI or SDAI remission at 6 months.

Relative contribution of the secondary ACR components to ACR20/50/70 response rates

Among ACR20 responders, PhGA contributed most to ACR20 response rate and CRP contributing the least. Among ACR50 responders, PtGA contributed most to ACR50 response rate in the csDMARD group, PhGA in TNFi, and pain in the TOFA group. CRP contributed the least for all medication groups. Among ACR70 responders, PhGA contributed most to ACR70 response rate in the csDMARD group and TNFi and pain in the TOFA group. CRP contributing the least for all medication groups (Supplementary Fig. S1).

Advanced analysis

Table III shows comparison between three medications on ACR20/50/70 response achievement, and at least 20/50/70% in primary components of ACR after adjusting for potential confounders. There was no statistically significant difference in impact of three

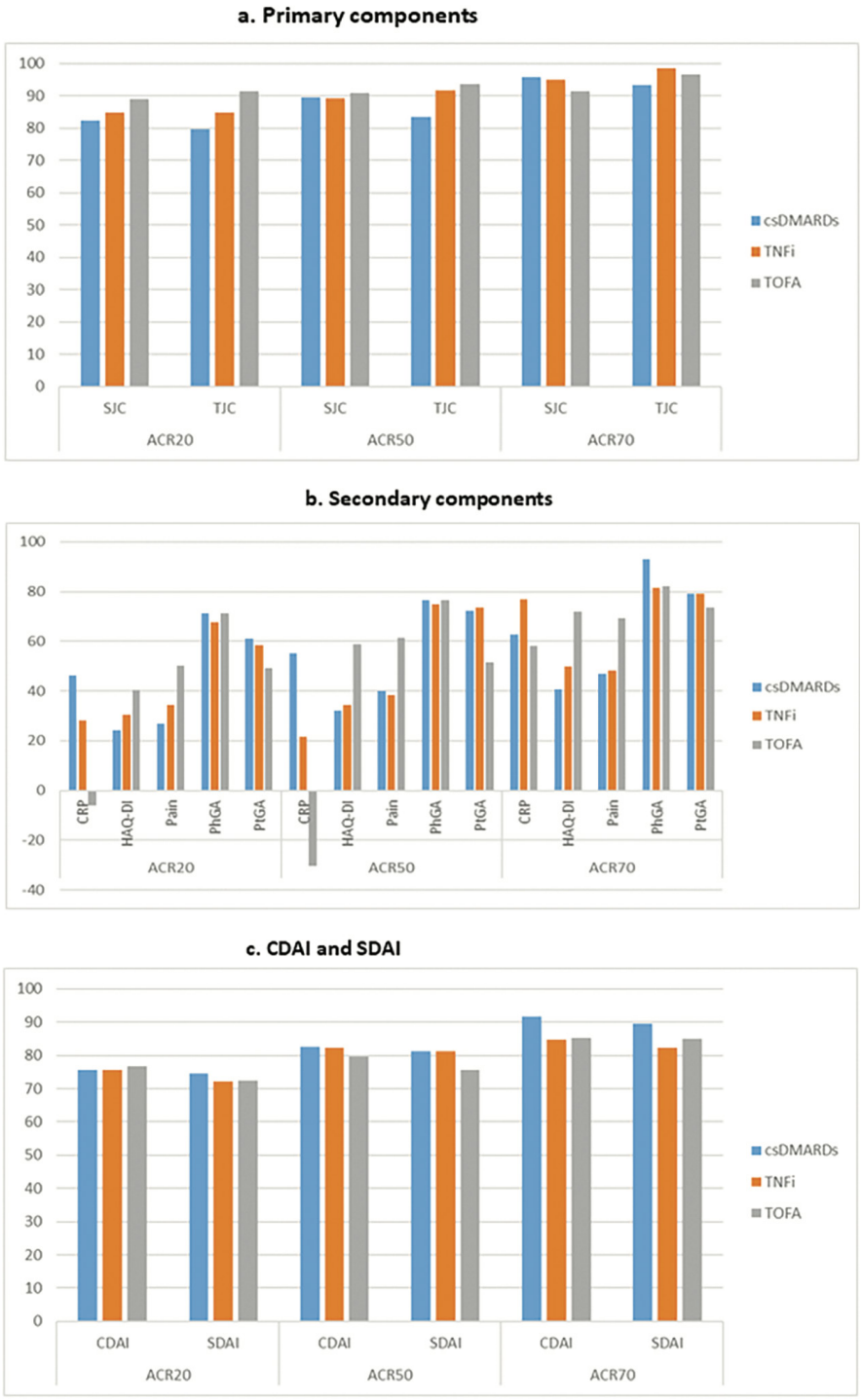

Fig. 2. Mean percentage improvement in ACR components in those patients who achieved an ACR20/50/70 at month 6.

medication class on these outcomes. For example, ACR20 response was 68% and 33% higher in the csDMARD (adjORs: 1.68; 95%CI: 0.95–2.98) and TNFi (adjORs: 1.33; 95%CI: 0.79–2.22), respectively compared to the TOFA group but it was not statistically significant. In contrast, numerically ACR70 was lower in the csDMARD group (adjORs: 0.77; 95%CI: 0.27–2.21) and TNFi (adjORs: 0.91; 95%CI: 0.36–2.29) compared to TOFA.

Regarding achievement in secondary components of ACR20/50/70, proportion of patients in the csDMARD group who achieved to at least 70% in physician global assessment was significantly two-fold higher compared to the TOFA group (adjORs: 2.00; 95%CI: 1.25–3.19). In contrast, the proportion of patients with at least 20% achievement in pain was significantly lower in the csDMARD compared to the TOFA group (adjORs: 0.62; 95%CI: 0.39–0.98) (Table IV). Similarly, a significantly lower proportion of patients in the TNFi group achieved to at least 50% improvement in pain (adjORs: 0.64; 95%CI: 0.44–0.93) compared to the TOFA group.

TNFi group also showed a lower at least 70% improvement in patient global assessment (adjORs: 0.53; 95%CI: 0.35–0.81) and at least 70% improvement in HAQ-DI (adjORs: 0.59; 95%CI: 0.35–0.99) compared to the TOFA group (Table IV).

Sensitivity analysis

We repeated analysis in a sub cohort of patients by excluding those with prior biologic use. Compared to TNFi class, ACR20/50/70 response and SDAI/CDAI LDA or remission rate were higher in the TOFA group at 6 months after initiation (Suppl. Fig. S2). ≥20/50/70% improvement rates in the TOFA group were also higher for primary and secondary components except ≥70% improvement in CRP and PtGA which were higher in TNFi class (Suppl. Fig. S3).

Discussion

In this real-world data study, we investigated the impact of different class of treatment on ACR20/50/70 primary and secondary components, SDAI and CDAI scores at 6 months after treatment initiation. The ACR response criteria for rheumatoid arthritis have been widely adopted as measures of medication efficacy in clinical trials (11, 12) but never used in clinical practice if not for research purposes. Questions were raised as to whether an ACR20 response represented a clinically significant improvement, given that 20% represents a relatively modest change in measures of RA activity, and preferred the more demanding responses of 50% or 70% (13, 14). However, this analysis showed that the average improvement in SJC and TJC exceeded 80% in the ACR20 responder group. For ACR70

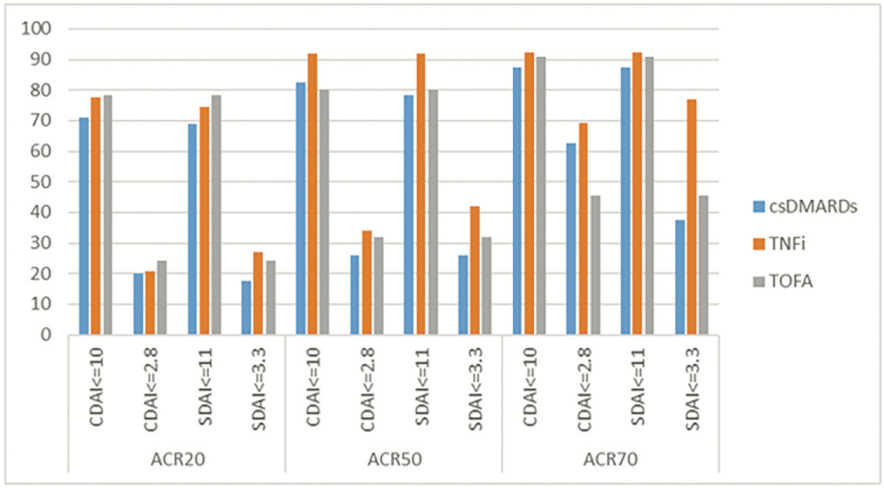

Fig. 3. Proportion of SDAI/CDAI LDA and remission in ACR20/50/70 responders at month 6.

responders, the mean improvement observed for SJC and TCJ is between 90–100%, which may be considered clinically significant if the aim is to achieve an absence of objective inflammatory sign on physical examination.

In these databases, the ACR20/50 response was lower in the TOFA group than in the TNFi and csDMARD group, but the ACR70 response was similar between treatment classes. Previous RCT studies showed that ACR20/50/70 were higher in the TOFA group than in the placebo group and numerically similar compared with adalimumab (9, 15-17). However, after adjusting for potential confounders including prior use of biologic, there was no statistically significant difference in ACR20/50/70 response between the three medication classes. The results of descriptive sensitivity analysis on the biologic naive sub cohort also showed that TOFA was doing better than TNFi (Suppl. Fig. S2). We found that ≥20/50/70% improvement in primary and secondary components surpassed the ACR20/50/70 response rate regardless of treatment class. Improvement ≥20/50/70% at 6 months in the physician-reported components was also found to be higher than in the patient-reported components. Among secondary components, ≥20/50/70% improvement was the highest for PhGA and the lowest for HAQ-DI. Interestingly, the difference between PhGA and PtGA decreases for ACR50 and 70 responders. All these findings are consistent with results from a recent *post-hoc* analysis using RCT data when they looked at these outcomes over 6 months (9). The least achievement in HAQ-DI can be related to a prior irreversible physical disability status particularly in patients with longer disease duration. As demonstrated in the same *post-hoc* analysis (9), HAQ-DI is the ACR score component that most limits the achievement of clinical response.

Similar to the study by Bessette *et al*. (9), in ACR20/50/70 responders, the mean percentage of improvement in the ACR components exceeded 20/50/70%, respectively, at month 6. In their analysis of the TOFA clinical trial data, only mean CRP was not improved in the TOFA group. The authors mentioned that this observation was related to outliers in the TOFA groups, and that the median percentage improvements in CRP from baseline were similar in all active treatment groups. We also found that the mean percentage improvement for PtGA was lower for ACR20/50/70 responders in the TOFA group. This finding can be explained by the higher number of prior biologic use and more severe disease activity at the baseline for the TOFA group. In contrast, the mean percentage improvement of pain and HAQ-DI in the TOFA group were higher compared to other treatment groups for ACR20/50/70 responders. In multivariable analysis, we showed that TOFA is doing better than TNFi for 70% improvement in patient global assessment and HAQ-DI. It has been shown that JAKi may have a more pronounced effect on pain than TNFi (18, 19).

The mean percentage improvement of CDAI and SDAI scores in 6 months was between 70–80% and 80–90% of

Table III. Adjusted comparison of ACR20/50/70 and at least 20/50/70% improvement in primary components between medication class in at 6 months after treatment.

	n	Event	csDMARDs OR (95% CI)	TNFi OR (95% CI)	TOFA
ACR response					
ACR20	897	133	1.68 (0.95-2.98)	1.33 (0.79-2.22)	Ref
ACR50	897	79	1.24 (0.62-2.48)	1.14 (0.62-2.12)	Ref
ACR70	897	31	0.77 (0.27-2.21)	0.91 (0.36-2.29)	Ref
Primary components of ACR					Ref
At least 20% improvement in tender joint counts	1025	331	1.07 (0.72-1.59)	0.99 (0.70-1.42)	Ref
At least 50% improvement in tender joint counts	1025	599	0.92 (0.63-1.35)	0.88 (0.63-1.23)	Ref
At least 70% improvement in tender joint counts	1025	471	0.88 (0.61-1.29)	1.05 (0.75-1.46)	Ref
at least 20% improvement in swollen joint counts	1052	370	1.04 (0.71-1.53)	1.05 (0.75-1.47)	Ref
at least 50% improvement in swollen joint counts	1052	643	1.16 (0.76-1.77)	1.14 (0.79-1.63)	Ref
at least 70% improvement in swollen joint counts	1052	501	1.14 (0.76-1.72)	1.07 (0.75-1.53)	Ref

Table IV. Adjusted comparison of at least 20/50/70% improvement in secondary components between medication class in at 6 months after treatment.

	n	Event	csDMARDs OR (95% CI)	TNFi OR (95% CI)	TOFA
Secondary components of ACR					
At least 20% improvement physician global assessment	1033	317	1.27 (0.85-1.89)	1.05 (0.73-1.50)	Ref
At least 50% improvement in physician global assessment	1033	479	1.38 (0.91-2.10)	0.97 (0.68-1.39)	Ref
At least 70% improvement in physician global assessment	1033	287	**2.00 (1.25-3.19)**	1.35 (0.89-2.03)	Ref
At least 20% improvement patient global assessment	1049	267	0.77 (0.27-2.21)	0.91 (0.36-2.29)	Ref
At least 50% improvement in patient global assessment	1049	362	1.31 (0.89-1.94)	1.08 (0.77-1.53)	Ref
At least 70% improvement in patient global assessment	1049	214	1.31 (0.85-2.02)	**0.53 (0.35-0.81)**	Ref
At least 20% improvement in HAQ-DI	1007	153	0.67 (0.40-1.11)	0.73 (0.47-1.14)	Ref
At least 50% improvement in HAQ-DI	1007	172	0.87 (0.48-1.55)	0.78 (0.48-1.29)	Ref
At least 70% improvement in HAQ-DI	1007	106	0.61 (0.34-1.08)	**0.59 (0.35-0.99)**	Ref
At least 20% improvement in pain	1017	205	**0.62 (0.39-0.98)**	0.69 (0.46-1.02)	Ref
At least 50% improvement in pain	1017	246	0.72 (0.47-1.10)	**0.64 (0.44-0.93)**	Ref
at least 70% improvement in pain	1017	140	1.04 (0.62-1.73)	0.80 (0.50-1.28)	Ref
At least 20% improvement in CRP	1041	249	1.11 (0.72-1.72)	1.23 (0.84-1.80)	Ref
At least 20% improvement in CRP	1041	379	1.23 (0.83-1.81)	1.38 (0.98-1.94)	Ref
At least 70% improvement in CRP	1041	242	1.27 (0.81-1.99)	1.46 (0.99-2.15)	Ref

ACR20 and ACR50 responders, respectively. These results show that the correlation between the ACR response and the change observed on the CDAI and SDAI is poor. Among ACR20/50/70 responders, between 70–90% and 20–70% of patients achieved CDAI LDA and remission across the three-medication group respectively. Bessette *et al*. showed that 38.2–52.0% of ACR20 responders and 61.4–79.5% of ACR50 achieved to LDA or remission at 3 months based on CDAI or SDAI (9). The proportion of ACR70 responders who achieved remission was higher in our study (40.0–75.0%) compared to the Bessette *et al*. study (23–45% at 3 months) suggesting 6 months treatment may be a better timeline for measuring treatment effectiveness (achieving remission) as physicians expect to see a CDAI/SDAI remission state in correspondence to an ACR70 response. Nevertheless, ACR70 response is not equivalent to clinical remission for many patients.

Our study was a descriptive and statistical observational analysis comparing the impact of different class of treatment on ACR components improvement. We applied a formal statistical testing and adjusted for potential confounders (*e.g*. age, gender, smoking status, education, disease duration, seropositive factors prior use of biologics, and concurrent steroid use). The adjusted results confirmed that TOFA is better at achieving pain and PROs compared to csDMARD and TNFi treatment.

As a limitation of this study, we cannot rule out the effects of unmeasured factors. Patients lost to follow-up and missed values of ACR components may also have influenced the results. We analysed data over 6 months, however, there may some longer-term impact of treatments on disease outcomes.

In conclusion, in this real-world practice analysis, physician-reported measures (TJC, SJC, and PhGA) contribute slightly more to overall ACR20/50/70 responses, compared with patient-reported outcomes (PtGA, Pain and HAQ-DI). In the ACR20 response group, a lower-level outcome, the improvement of the SJC and TJC, exceeded 80%. Pain was the most important factor in achieving an ACR50 for patients treated with TOFA, possibly reflecting the different effects of JAKi on pain.

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