

Real-World Tocilizumab Use in Patients with Rheumatoid Arthritis in Canada: 12-Month Results From an Observational, Noninterventional Study

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ABSTRACT

Introduction: This study was conducted to observe patterns of use of the interleukin-6 receptor-alpha inhibitor tocilizumab in routine clinical practice in patients with rheumatoid arthritis (RA).

Methods: This was a 12-month noninterventional, observational study in adult patients

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with RA who initiated tocilizumab in routine practice in Canada according to the local product monograph. The primary end point was the proportion of patients receiving tocilizumab at 6 months. Secondary end points were treatment patterns, effectiveness, and safety of tocilizumab over 12 months.

Results: Of 200 patients who initiated tocilizumab (91.0% at 8 mg/kg), 67 (33.5%) received tocilizumab monotherapy and 133 (66.5%) received tocilizumab combined with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Kaplan–Meier analysis estimated that 85% (95% CI 74–92%) of monotherapy and 89% (95% CI 82–93%) of combination therapy patients continued to receive tocilizumab at 6 months (log-rank $p = 0.0888$). During the observation period, 12 (17.9%) monotherapy and 27 (20.3%) combination therapy patients withdrew from the study. At month 12, 58.5% in the monotherapy group and 59.3% in the combination therapy group achieved Disease Activity Score at 28 joints remission (≤ 2.6), 25.6% and 24.7% achieved Simplified Disease Activity Index remission (≤ 3.3), and 18.2% and 22.3% achieved Clinical Disease Activity Index remission (≤ 2.8), respectively. Rates of serious adverse events and serious infections were found in 29.6/100 patient-years (PY) and 3.1/100 PY, respectively, for monotherapy and 19.2/100 PY and 4.8/100 PY, respectively, for combination therapy.

Conclusions: Patients initiating tocilizumab in routine practice had comparable effectiveness and safety outcomes regardless of whether they received tocilizumab as monotherapy or as combination therapy with csDMARDs.

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INTRODUCTION

Recommendations from the Canadian Rheumatology Association for the management of rheumatoid arthritis (RA) state that remission or low disease activity (LDA) should be targeted and that therapy should be adjusted every 3–6 months to achieve this goal [1]. Biological disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFi) abatacept and tocilizumab, in combination with methotrexate (MTX), are recommended to treat patients with poor prognostic factors or patients who do not respond to conventional synthetic DMARDs (csDMARDs) [1–3]. However, up to 37% of RA patients may not be able to continue treatment with MTX because of intolerance, and approximately one-third of patients receive bDMARD monotherapy [4–6].

Tocilizumab is a humanized anti-human monoclonal antibody against the interleukin-6 receptor alpha subunit (IL-6R α), which blocks IL-6 signaling [7, 8]. In Canada, tocilizumab is approved for the treatment of RA and polyarticular and systemic juvenile idiopathic arthritis. The Canadian product monograph states that tocilizumab should be administered in combination with MTX or other csDMARDs or as monotherapy in cases of intolerance or contraindication to MTX. Recommended dosing for intravenous tocilizumab is 4 mg/kg every 4 weeks, increased to 8 mg/kg based on

clinical response. In phase 3/4 clinical trials, tocilizumab was effective for treating the signs and symptoms of RA in combination with MTX/csDMARDs [9–13] and as monotherapy [13–15]. Clinical practice studies confirmed the effectiveness and safety of tocilizumab monotherapy and combination therapy in the real world [16, 17].

ACT-UP CARE (ACT-UP Canadian Physician Observance of RA Patients on Tocilizumab) is part of an ongoing, multinational, observational study. Patterns of use of tocilizumab monotherapy or combination therapy with csDMARDs, including persistence on the drug and adherence to the licensed Canadian product monograph [18], were observed in routine clinical practice between February 2012 and October 2014 in RA patients.

METHODS

Study Design

ACT-UP CARE, part of a global umbrella study to observe tocilizumab use initiated in routine clinical practice [19], was a 12-month, non-interventional, postmarketing, multicenter, observational study conducted at 26 sites across Canada. No interventional procedures or visits outside routine practice were mandated; tocilizumab and concomitant medications were prescribed, according to the investigator's judgment and the Canadian product monograph [18], to adult patients with moderate-to-severe RA whose physicians decided to commence treatment with tocilizumab. Enrolled patients provided written informed consent approved by the institutional review boards or independent ethics committees. Patients who provided informed consent and who received at least one dose of tocilizumab in the Canadian arm of ACT-UP were included. Patients were grouped into those who received tocilizumab in combination with csDMARDs and those who received tocilizumab monotherapy. In an exploratory subanalysis, patients were grouped into csDMARD-inadequate responders (IR) and TNFi-IR.

Assessments

The baseline visit was the last valid assessment before the first dose of tocilizumab, which might not have coincided with the enrollment visit. The primary end point was the proportion of patients receiving tocilizumab at 6 months. Because the treatment regimen required infusion every 4 weeks, predefined assessment windows between study days 154 (24 weeks) and 197 (28 weeks) were considered to capture infusions that might have fallen outside a 6-month visit.

The proportion of patients receiving tocilizumab at 12 months was a secondary end point; predefined assessment windows between study days 351 (50 weeks) and 379 (54 weeks) were considered.

Other secondary end points were treatment patterns over time (3 months, 6 months, 9 months, and 12 months), including dose modifications, rates, and reasons for dose modification; physician compliance with the product monograph–recommended dosing regimen and management of adverse events (AEs); proportions of patients receiving tocilizumab monotherapy (3 months, 6 months, 9 months, and 12 months), including reasons for monotherapy at baseline and reasons for csDMARD withdrawal; effectiveness over 52 weeks, including change in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), swollen joint count, tender joint count, Disease Activity Score based on 28 joints (DAS28), patient-reported outcomes (PROs) (on a visual analog scale [VAS] evaluating pain, fatigue, and morning stiffness), European League Against Rheumatism (EULAR) responses, Clinical Disease Activity Index (CDAI)/Simplified Disease Activity Index (SDAI), prevalence, and severity of extra-articular manifestations; change in concomitant csDMARDs and rationale and compliance with csDMARD and corticosteroid treatment; and safety over 52 weeks, including AEs, serious AEs (SAEs), rates of SAEs, and serious infections per 100 patient-years (PY) of exposure, cardiovascular events, and laboratory abnormalities. SAEs were determined by the investigator and were considered

as any experience suggesting a significant hazard, contraindication, side effect, or precaution that resulted in death, was life threatening, necessitated hospitalization, resulted in persistent or significant disability or birth defect, or required intervention to prevent one of these events.

Statistical Analysis

A sample size of 200 was deemed sufficient for valid inferences to Canadian RA patients treated with tocilizumab based on an estimated rate for the primary outcome measure—6-month persistence of treatment—of 75% [95% confidence interval (CI) 69–81%] and estimated rates for effectiveness measures of 73% (95% CI 66–79%) for EULAR good/moderate response and 25% (95% CI 19–31%) for DAS28 < 2.6 according to previous studies [9–11]. All assessments except safety were performed in the full analysis set, which consisted of all patients enrolled. All results were based on available patient data, and there was no imputation for missing data. The safety population consisted of all patients who received at least one dose of tocilizumab. Continuous variables were summarized using descriptive statistics (number of subjects, mean, standard deviation, or standard error). Categorical variables were summarized using frequencies and percentages. Unless otherwise specified, all statistical tests were two-sided and were performed with a 5% alpha error rate without correction for multiplicity. CIs for the proportions of patients receiving tocilizumab were computed based on the Clopper–Pearson method, and *p* values were determined using Fisher’s exact test.

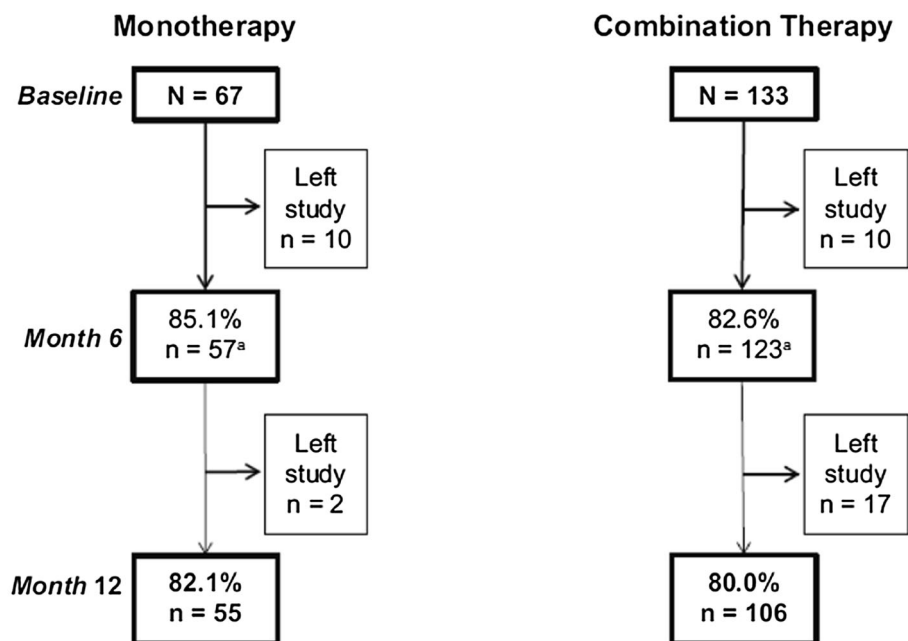
Post hoc analysis was conducted to examine baseline demographics and disease characteristics in patients who discontinued tocilizumab for lack of efficacy between baseline and month 6 (primary failure) and between month 6 and month 12 (secondary failure). Primary and secondary failures were defined arbitrarily by the clinician and according to the time of failure.

RESULTS

Patients

Overall, 200 patients were enrolled from 26 sites across Canada and were included in the full analysis set (Fig. 1). The safety population included 198 patients because two patients did not receive tocilizumab. In the full analysis set, 67 patients (33.5%) received tocilizumab monotherapy and 133 patients (66.5%) received tocilizumab in combination with csDMARDs at baseline (19

patients in the combination therapy group discontinued csDMARDs during the study and continued tocilizumab monotherapy but were included in the combination therapy group). Ten patients in each group left the study during the first 6 months; 85.1% of monotherapy patients and 92.5% of combination therapy patients remained in the study at month 6 (including patients who discontinued tocilizumab but continued study observation). Two patients in the monotherapy group and 17 in the combination therapy group left the study between months 6



Reasons for leaving the study, n patients	Monotherapy	Combination therapy
Adverse event	5	6
Death	1	1
Lack of efficacy	1	12
Withdrawal of consent	4	4
Lost to follow-up	0	1
Other	1	3

Fig. 1 Patient disposition over 12 months (full analysis set; $N = 200$). Patients could have discontinued tocilizumab but remained in the study. *Asterisk* Including six

patients from each group who missed the month 6 visit but attended the month 12 visit

and 12; 82.1% of monotherapy patients and 79.7% of combination therapy patients remained in the study at month 12. The most common reason for study withdrawal in the monotherapy group was AEs (five patients), whereas the most common reasons for withdrawal in the combination therapy group were lack of efficacy (12 patients) and AEs (six patients).

Baseline characteristics were similar between monotherapy and combination therapy groups except for a higher incidence of previous RA-related surgical procedures and higher Patient Global Assessment of Disease Activity (PtGA) VAS scores in the monotherapy group (Table 1). Patients had advanced RA; the mean (\pm SD) disease duration at baseline was 13.8 (\pm 11.1) years in the monotherapy group and 12.0 (\pm 10.0) years in the combination therapy group. As expected, patients with advanced disease requiring biological treatment had comorbidities, including cardiovascular risk factors. Overall, patients in both groups had stable cholesterol profiles, and nine of 67 (13.4%) patients and 13 of 133 (9.8%) patients in the monotherapy group and combination therapy group, respectively, were concomitantly treated with statins. Baseline demographics and disease characteristics were generally comparable with those of the ACT-UP global study, in which 37.9% of patients received tocilizumab as monotherapy [19]. Framingham risk category at baseline was available for 57 tocilizumab-treated patients; 30 (52.6%) had low risk (< 10%), 21 (36.8%) had moderate risk (10–19%), and six (10.5%) had high risk (\geq 20%).

Tocilizumab Treatment

Overall, 173 (87.4%; 95% CI 81.9–91.7%) patients remained in the study and were still receiving tocilizumab infusions at month 6 (primary end point), and 159 (80.3%; 95% CI 74.1–85.6%) remained in the study and were still receiving tocilizumab at month 12. Post hoc analysis of the 13 patients who discontinued tocilizumab because of lack of efficacy between baseline and 12 months revealed that nine discontinued between baseline and month

6 (primary failure) and four discontinued between month 6 and month 12 (secondary failure). Although the patient numbers are too small for statistical comparisons, trends showed that patients with secondary failure were older and experienced longer durations of disease, more structural joint damage, and worse PRO scores—including Patient Pain VAS, PtGA VAS, and Fatigue VAS—than those with primary failure or patients still receiving tocilizumab at month 12. Objective measures, such as disease activity, were comparable between patients with primary failure, patients with secondary failure and patients still receiving tocilizumab at month 12 (Supplementary Table S1).

The most common reason for patients to receive tocilizumab monotherapy rather than combination therapy was intolerance of csDMARDs (34.3%). The next most common reasons were physician decision (26.9%), proven efficacy of monotherapy (9.0%), standard of care (7.5%), biological inadequate response/failure (6.0%), patient decision (6.0%), and other (10.5%).

Proportions of patients who remained in the study and were receiving tocilizumab at month 6 (primary end point) and month 12 were not significantly different regarding monotherapy and combination therapy with csDMARDs. Among monotherapy patients, 56 of 67 (83.5%) continued to receive tocilizumab at month 6 and 54 of 67 (81.0%) continued to receive tocilizumab at month 12. Among combination therapy patients, 117 of 133 (88.0%) continued to receive tocilizumab at month 6 and 105 of 133 (78.9%) continued to receive tocilizumab at month 12. Kaplan–Meier analysis estimated that 85% (95% CI 74–92%) of monotherapy patients and 89% (95% CI 82–93%) of combination therapy patients continued to receive tocilizumab at month 6 (log rank, $p = 0.0888$).

Most of the total patient population ($n = 158$; 79.0%) had previously received other biologicals before initiating tocilizumab, and these patients were balanced between the monotherapy (53/67; 79.1%) and the combination therapy (105/133; 78.9%) groups. Among the 53 monotherapy patients, 43.4% previously received one biological, 30.2% received two biologicals, and 26.4% received

Table 1 Baseline demographics and disease characteristics

Parameter	Monotherapy <i>N</i> = 67	Combination therapy, <i>N</i> = 133	<i>p</i> value
Age, years	55.2 (14.0)	55.6 (13.3)	0.841
Female, <i>n/N</i> (%)	53/67 (79.1)	107/133 (80.5)	0.853
Disease duration, years	13.8 (11.1)	12.0 (10.0)	0.379
	<i>n</i> = 65	<i>n</i> = 132	
TJC28	12.5 (7.0)	12.6 (7.2)	0.905
	<i>n</i> = 65	<i>n</i> = 129	
SJC28	9.8 (4.8)	9.2 (5.5)	0.415
	<i>n</i> = 65	<i>n</i> = 129	
PtGA, VAS mm	67.3 (20.8)	60.1 (21.4)	0.006 ^b
	<i>n</i> = 67	<i>n</i> = 132	
PGA, VAS mm	65.1 (21.4)	60.0 (22.7)	0.051
	<i>n</i> = 67	<i>n</i> = 132	
CRP, mg/l	15.5 (17.2)	21.8 (43.8)	0.309
	<i>n</i> = 57	<i>n</i> = 119	
ESR, mm/h	26.9 (20.1)	27.3 (23.4)	0.623
	<i>n</i> = 52	<i>n</i> = 109	
Pain, VAS mm	65.5 (23.2)	62.2 (22.7)	0.241
	<i>n</i> = 65	<i>n</i> = 130	
Morning stiffness, VAS mm	60.5 (22.9)	57.3 (22.9)	0.357
	<i>n</i> = 65	<i>n</i> = 129	
Fatigue, VAS mm	66.1 (23.3)	61.1 (24.7)	0.096
	<i>n</i> = 65	<i>n</i> = 129	
DAS28	5.7 (1.0)	5.6 (1.3)	0.477
	<i>n</i> = 63	<i>n</i> = 124	
SDAI	37.3 (11.2)	35.6 (14.8)	0.268
	<i>n</i> = 55	<i>n</i> = 115	
CDAI	35.7 (11.8)	33.8 (13.1)	0.282
	<i>n</i> = 65	<i>n</i> = 129	
RF positive, <i>n/N</i> (%)	34/67 (50.7)	76/133 (57.1)	0.600
Anti-CCP positive, <i>n/N</i> (%)	17/67 (25.4)	39/133 (29.3)	0.202
Family history of coronary disease, <i>n/N</i> (%)	18/67 (26.9)	34/129 (26.4)	> 0.999
Current or past smoker, <i>n/N</i> (%)	29/67 (43.3)	60/133 (45.1)	0.885 ^a

Table 1 continued

Parameter	Monotherapy <i>N</i> = 67	Combination therapy, <i>N</i> = 133	<i>p</i> value
Previous RA-related surgical procedure, <i>n/N</i> (%)	23/67 (34.3)	25/133 (18.8)	0.022 ^b
Structural joint damage, <i>n/N</i> (%)	36/67 (53.7)	67/133 (50.4)	0.764
Cardiovascular risk factors, <i>n/N</i> (%)			
Cerebrovascular disease	1/67 (1.5)	3/132 (2.3)	> 0.999
Coronary artery disease	6/67 (9.0)	13/132 (9.8)	> 0.999
Diabetes, type 1 or 2	8/67 (11.9)	18/132 (13.6)	0.826
Hyperlipidemia	13/67 (19.4)	30/132 (22.7)	0.716
Hypertension	28/67 (41.8)	45/132 (34.1)	0.351

Data are presented as mean (SD) unless otherwise stated. *N*'s are the number of patients with baseline data available for each variable

p value was assessed using nonparametric Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables

^a Between all smoking status groups: current smoker, past smoker, and non-smoker

^b Denotes statistical difference ($p < 0.05$) between groups

CCP cyclic citrullinated peptide, *CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *DAS28* Disease Activity Score using 28 joints, *ESR* erythrocyte sedimentation rate, *PGA* Physician Global Assessment of disease activity, *PtGA* patient global assessment of disease activity, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SDAI* Simplified Disease Activity Index, *SJC28* swollen joint count at 28 joints, *TJC28* tender joint count at 28 joints, *VAS* visual analog scale

three or more biologicals. Among the 105 combination therapy patients, the proportions were 52.4, 23.8, and 23.8%, respectively, with no significant difference compared with the monotherapy patients ($p = 0.542$). The most common previous biological was etanercept, used by 47.8% of monotherapy patients and 34.6% of combination therapy patients ($p = 0.091$). Other previous biologicals were adalimumab (26.9 vs. 24.1%; $p = 0.730$), infliximab (22.4 vs. 29.3%; $p = 0.317$), certolizumab (20.9 vs. 13.5%; $p = 0.220$), abatacept (19.4 vs. 18.8%; $p > 0.999$), rituximab (9.0 vs. 9.0%; $p > 0.999$), and golimumab (1.5 vs. 11.3%; $p = 0.014$). The most common reason for discontinuing previous biological therapy was lack of efficacy (75.2 vs. 75.9%), followed by intolerance (13.9 vs. 11.5%) and patient decision (2.0 vs. 1.0%); 8.9% of monotherapy and 11.5% of combination therapy patients discontinued for other/unknown reasons.

Among patients who received tocilizumab in combination with previous and ongoing

csDMARD/s ($n = 125$; although eight patients were assigned to the combination therapy group, the type of csDMARD was unknown), 75.2% received MTX, 34.6% received hydroxychloroquine, 15.0% received leflunomide, 8.3% received sulfasalazine, 3.0% received gold, 1.5% received azathioprine, and 0.8% received cyclosporine.

Most patients started tocilizumab at 8 mg/kg (monotherapy group, 92.5%; combination therapy group, 90.2%). Tocilizumab was initiated at 4 mg/kg in four monotherapy patients (6.0%) and 12 combination therapy patients (9.0%). One patient in the monotherapy group reported a starting dose of 7 mg/kg, and one patient in the combination therapy group reported a starting dose of 5 mg/kg, which may reflect logistical reasons for dosing rather than clinical rationale. At month 6, 54 monotherapy patients (96.4%) and 105 combination therapy patients (86.1%) were receiving stable doses. At month 12, 47 monotherapy patients (95.9%) and 90 combination therapy patients (93.8%) were receiving stable doses.

Effectiveness

Both the monotherapy and the combination therapy groups demonstrated a decrease in DAS28 over time (Fig. 2). Mean \pm SD DAS28 decreased from baseline (5.7 ± 1.0 monotherapy, 5.6 ± 1.3 combination therapy) to month 3 (3.5 ± 1.6 monotherapy, 3.2 ± 1.5 combination therapy). Further decreases occurred through month 12 (2.7 ± 1.7 monotherapy, 2.4 ± 1.5 combination therapy). Rates of disease activity over time according to DAS28, SDAI, and CDAI criteria are shown in Fig. 3. Similar proportions of monotherapy (58.5%; 24/41) and combination therapy (59.3%; 48/81) patients achieved DAS28 remission ($\text{DAS28} \leq 2.6$) by month 12.

Safety

Proportions of patients with treatment-emergent AEs, tocilizumab discontinuations due to AEs, SAEs, and serious infections were similar between the monotherapy and combination

therapy groups (Table 2). Rates of SAEs were 29.6/100 PY in the monotherapy group and 19.2/100 PY in the combination therapy group, and rates of serious infection were 3.1/100 PY and 4.8/100 PY, respectively. Shifts in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, or both, from normal at baseline to greater than the upper limit of normal (ULN) during the study were observed in 30.9% of monotherapy and 45.2% of combination therapy patients, respectively. Most increases were from normal at baseline to $1\text{--}3 \times \text{ULN}$, with increases in ALT and AST $> 3 \times \text{ULN}$ not reported in any patients in the monotherapy group but reported in five and three patients, respectively, in the combination therapy group. Neutrophil counts declined from normal at baseline to between the lower limit of normal and $1.0 \times 10^9/\text{l}$ in 13.5% of monotherapy patients and 10.3% of combination therapy patients. Decreases in neutrophil counts to $0.5\text{--}1.0 \times 10^9/\text{l}$ were reported in 3.8 and 7.2% of patients, respectively, and shifts to $< 0.5 \times 10^9/\text{l}$ were reported in 3.8 and 7.2% of patients,

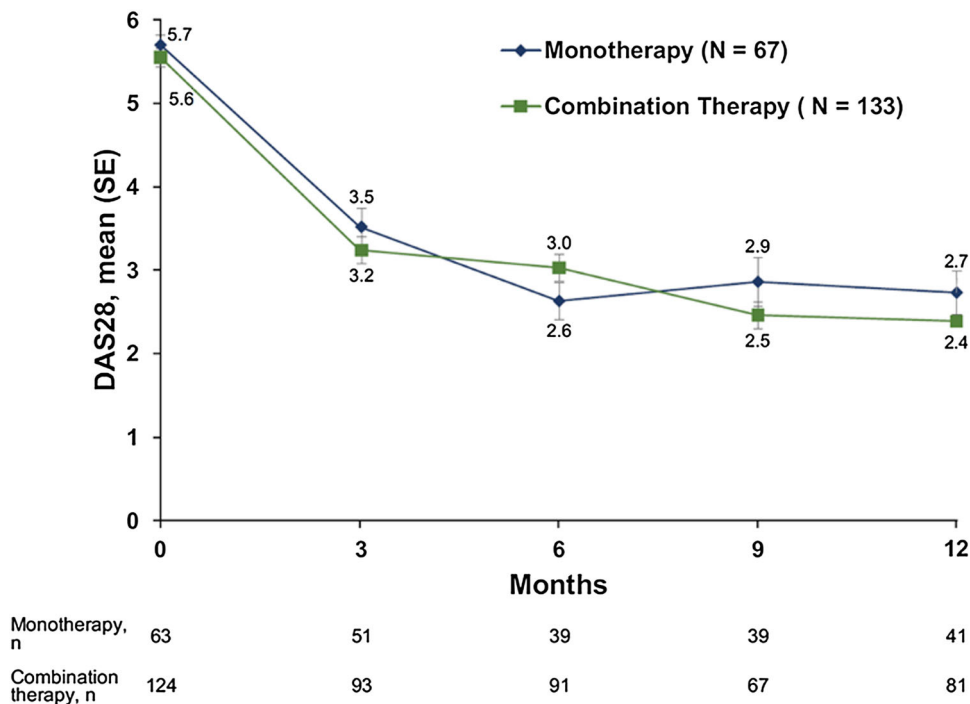


Fig. 2 Mean DAS28 over time. No statistical difference ($p > 0.05$) based on nonparametric Mann–Whitney U test between groups at all time points. *DAS28* Disease Activity Score Based on 28 joints, *SE* standard error

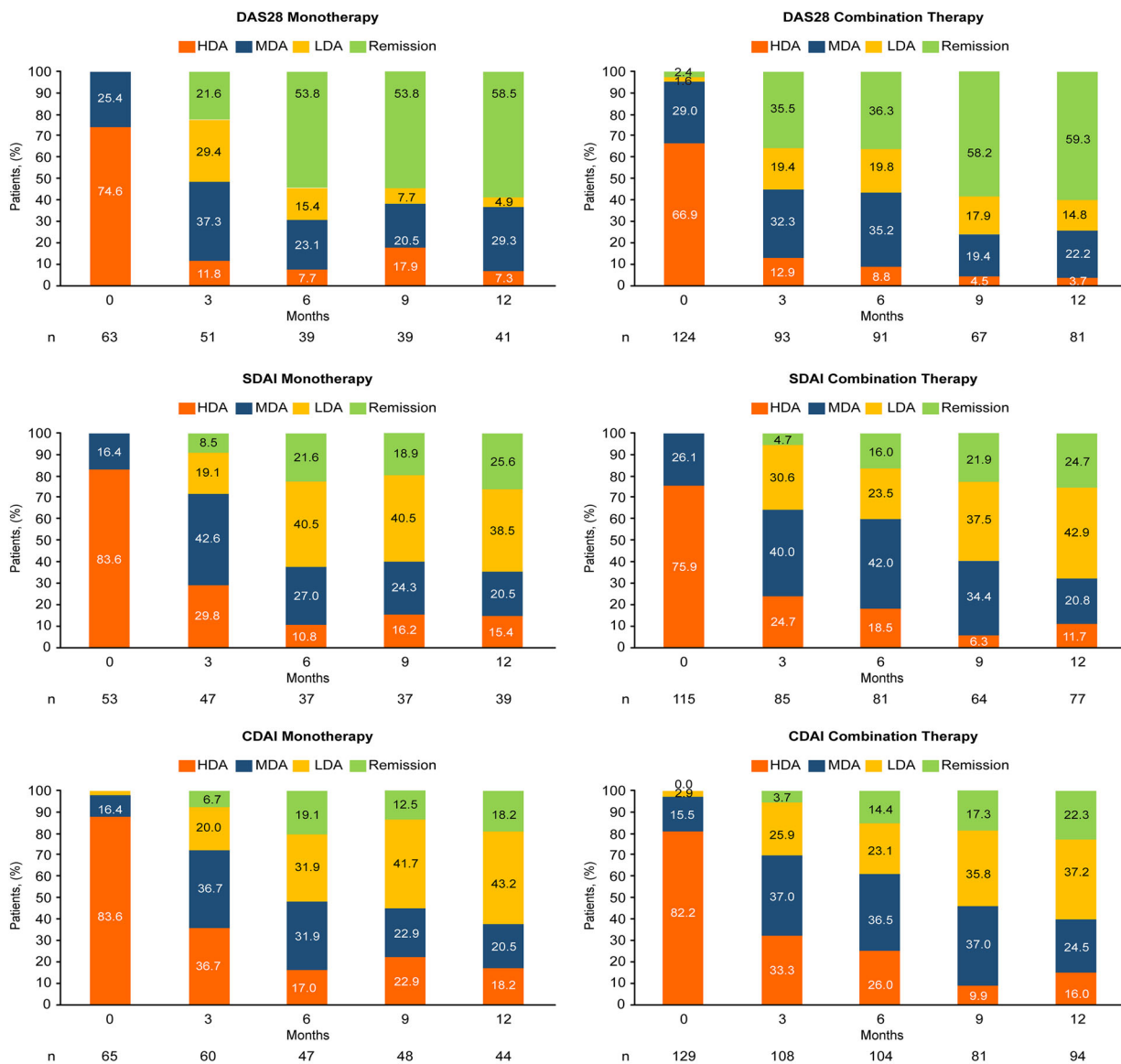


Fig. 3 Rates of disease activity states over time in monotherapy and combination therapy patients according to DAS28, SDAI, and CDAI criteria. *n* number of evaluable patients. DAS28: remission, ≤ 2.6 ; LDA, ≤ 3.2 ; MDA, ≤ 5.1 ; HDA, > 5.1 . SDAI: remission, ≤ 3.3 ; LDA, ≤ 11.0 ; MDA, ≤ 26.0 ; HDA, > 26.0 . CDAI:

≤ 2.8 ; LDA, ≤ 10.0 ; MDA, ≤ 22.0 ; HDA, > 22.0 . CDAI Clinical Disease Activity Index, DAS28 Disease Activity Score based on 28 joints, HDA high disease activity, LDA low disease activity, MDA moderate disease activity, SDAI Simplified Disease Activity Index

respectively (Table 2). Lipid levels (total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides) remained relatively stable over time (Supplementary Fig. S1). Two patients died during the study; one patient receiving combination therapy died of pneumonia and one

patient receiving monotherapy died of cervical instability in the neck, fat embolism, obstructive shock, and hip pseudotumor. Neither death was considered related to tocilizumab by the treating physician. No gastrointestinal perforations were reported.

Table 2 Safety over 12 months (safety population)

	Monotherapy <i>n</i> = 67	Combination therapy <i>N</i> = 131	All tocilizumab-treated patients <i>N</i> = 198
Adverse events			
Total TEAEs, <i>n</i>	175	380	555
Patients with ≥ 1 TEAE	60 (89.6)	106 (80.9)	166 (83.8)
Discontinuation due to AE	7 (10.4)	11 (8.4)	18 (9.1)
Total SAEs, <i>n</i> (rate per 100 PY)	19 (29.60/100 PY)	24 (19.22/100 PY)	43 (22.75/100 PY)
Patients with ≥ 1 SAE	13 (19.4)	18 (13.7)	31 (15.7)
Infection SAEs, <i>n</i> (rate per 100 PY)	2 (3.12/100 PY)	6 (4.80/100 PY)	8 (4.23/100 PY) ^d
Patients with ≥ 1 infection SAE	2 (3.0)	5 (3.8)	7 (3.5)
Deaths	1 (1.5) ^b	1 (0.8) ^c	2 (1.0)
Laboratory abnormalities, <i>n/N</i> ^a (%)			
AST shift from normal to			
1–3 \times ULN	4/50 (8.0)	20/94 (21.3)	24/144 (16.7)
3–5 \times ULN	0	2/94 (2.1)	2/144 (1.4)
> 5 \times ULN	0	1/94 (1.1)	1/144 (0.7)
ALT shift from normal to			
1–3 \times ULN	13/55 (23.6)	24/115 (20.9)	37/170 (21.8)
3–5 \times ULN	0	5/115 (4.3)	5/170 (2.9)
> 5 \times ULN	0	0	0
Neutrophils shift from normal to			
< LLN-1.0 $\times 10^9/l$	7/52 (13.5)	10/97 (10.3)	17/149 (11.4)
0.5–1.0 $\times 10^9/l$	2/52 (3.8)	7/97 (7.2)	9/149 (6.0)
< 0.5 $\times 10^9/l$	2/52 (3.8)	7/97 (7.2)	9/149 (6.0)

^a Based on available data for patients who had normal levels at baseline

^b Death due to cervical instability, fat embolism, obstructive shock, and hip pseudotumor

^c Death due to pneumonia

^d Two events of pneumonia and one event each of cellulitis, cystitis, postoperative wound infection, pyelonephritis, subcutaneous abscess, and urosepsis

Data are *n* (%) unless stated otherwise

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *LLN* lower limit of normal, *PY* patient-years, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *ULN* upper limit of normal

Exploratory Analysis in csDMARD-IR and Biological-IR Patients

At baseline, 51 patients (25.5%) were csDMARD-IR when they initiated tocilizumab

and 149 patients (74.5%) were biological-IR. After 6 months, 46 csDMARD-IR patients (90.2%) and 134 biological-IR patients (89.9%) remained in the study; after 12 months, 45 (88.2%) and 116 (77.8%) patients, respectively,

remained in the study. Among biological-IR patients, 65 of 78 patients (83.3%) whose single previous biological failed and 60 of 80 patients (75.0%) whose multiple previous biologicals failed were still receiving tocilizumab after 12 months. Among the 78 single-previous biological-IR patients, 20 of 23 monotherapy patients (87.0%) and 45 of 55 combination therapy patients (81.8%) were still receiving tocilizumab at month 12. Among the 80 multiple-previous biological-IR patients, 23 of 30 monotherapy patients (76.7%), and 37 of 50 combination therapy patients (74.0%) were still receiving tocilizumab at month 12. Proportions of patients achieving DAS28 remission or LDA at month 12 in the csDMARD-IR and biological-IR subgroups, respectively, were 67.6% (23/34) and 55.7% (49/88) for remission and 5.9% (2/34) and 13.6% (12/88) for LDA. Response rates over time from months 0 to 12 are shown in Fig. 4.

AEs were reported by 47 of 50 csDMARD-IR patients (94.0%) and 119 of 148 biological-IR patients (80.4%). SAEs were reported by 16.0 and 15.5% of patients, respectively. Discontinuation because of AEs was reported for two patients (4.0%) in the csDMARD-IR subgroup and 16 patients (10.8%) in the biological-IR subgroup. No serious infections were reported in csDMARD-IR patients, and eight serious infections were reported in seven biological-IR patients (two pneumonia and one each cellulitis, cystitis, postoperative wound infection, pyelonephritis, subcutaneous abscess, and urosepsis). Both reported deaths occurred in biological-IR patients.

DISCUSSION

The ACT-UP CARE study provides a snapshot of tocilizumab use in routine clinical practice over 12 months in the Canadian RA population between February 2012 and October 2014. Tocilizumab was received as monotherapy in 33.5% of patients in this study, consistent with observational studies estimating that one-third of RA patients treated with biologicals receive them as monotherapy [4–6]. The most common reason for receiving tocilizumab monotherapy

was intolerance of csDMARDs, highlighting the need for biological agents equally effective as monotherapy and combination therapy. Drug survival rates with tocilizumab were high after 6 months and were not statistically significantly different between tocilizumab monotherapy and combination therapy with csDMARDs, with 85% of monotherapy and 89% of combination therapy patients remaining in the study and continuing to receive tocilizumab at 6 months as assessed by Kaplan–Meier analysis ($p = 0.0888$).

These results are consistent with previous results of tocilizumab monotherapy and combination therapy in randomized controlled trials and in clinical practice. Proportions of patients completing 6 months of tocilizumab were 91.0% for monotherapy and 93.2% for combination therapy in a randomized controlled trial [20] and 87.9 and 87.1%, respectively, in an open-label study resembling clinical practice [16]. However, in the ACT-UP global umbrella study, fewer monotherapy patients (80%) than combination therapy patients (87%) were still receiving tocilizumab after 6 months ($p < 0.001$ for the comparison) [19]. In RA patients, higher persistence on TNFi was observed when received in combination with csDMARDs than as monotherapy; however, greater persistence with combination therapy may be attributed to increased effectiveness compared with TNFi monotherapy [21]. This is in contrast to the results of the current analyses, which did not demonstrate differences in efficacy between tocilizumab monotherapy and combination therapy. Comparisons between studies are hindered by differences in patient populations and study design; nevertheless, in an observational global comparative effectiveness study in csDMARD-IR RA patients, the 6-month drug survival rate in patients receiving tocilizumab (91%) was higher than in patients receiving TNFi (85%; $p < 0.001$ for the comparison) [19]. In ACT-UP CARE, the 25.5% of patients who were csDMARD-IR and the 74.5% who were biological-IR when they initiated tocilizumab had good tocilizumab survival rates. These results support those of the previous open-label study of tocilizumab resembling clinical practice that reported 89.8%

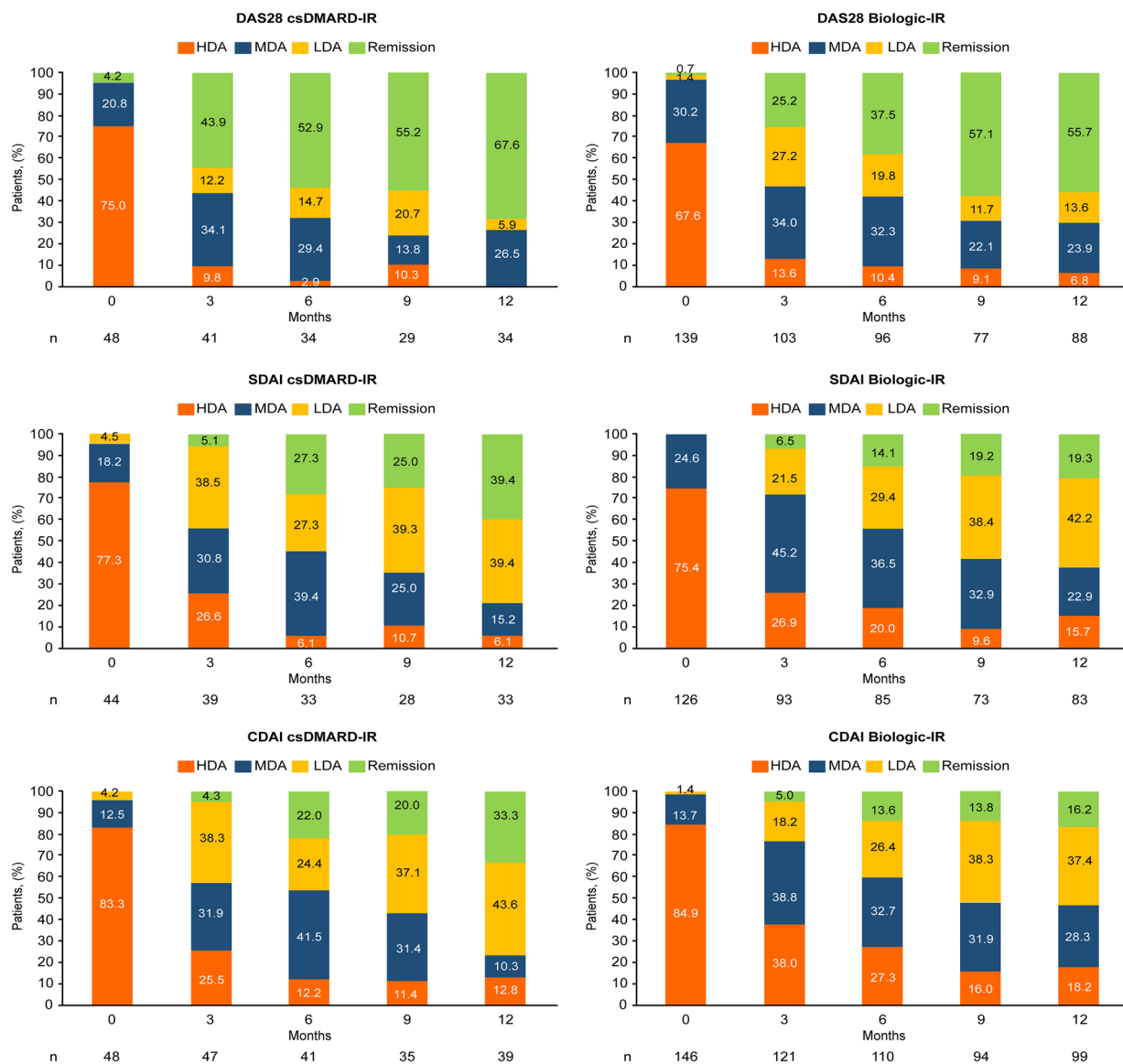


Fig. 4 Rates of disease activity over time in csDMARD-IR and biological-IR patients according to DAS28, SDAI, and CDAI criteria. *n* number of evaluable patients. DAS28: remission, ≤ 2.6 ; LDA, ≤ 3.2 ; MDA, ≤ 5.1 ; HDA, > 5.1 . SDAI: remission, ≤ 3.3 ; LDA, ≤ 11.0 ; MDA, ≤ 26.0 ; HDA, > 26.0 . CDAI: ≤ 2.8 ; LDA, ≤ 10.0 ; MDA, ≤ 22.0 ; HDA, > 22.0 . CDAI Clinical Disease

Activity Index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28* Disease Activity Score based on 28 joints, *HDA* high disease activity, *IR* inadequate responder, *LDA* low disease activity, *MDA* moderate disease activity, *SDAI* Simplified Disease Activity Index

of DMARD-IR and 83.7% of TNFi-IR patients completed 6 months of tocilizumab treatment [22]. In ACT-UP CARE, 87.0 and 81.8% of monotherapy and combination therapy patients, respectively, were still receiving tocilizumab after 1 year of treatment at comparable

rates regardless of whether one or multiple previous biological agents failed.

Effectiveness outcomes, including high hurdle measures such as rates of remission and LDA—targets recommended in American College of Rheumatology (ACR)/EULAR treat-to-

target recommendations [23]—did not appear to differ between tocilizumab monotherapy and combination therapy groups in the current study, although statistical comparisons were not performed. After 1 year, DAS28 remission was achieved by 58.5% of monotherapy and 59.3% of combination therapy patients, respectively, SDAI remission by 25.6 and 24.7%, respectively, and CDAI remission by 18.2 and 22.3%, respectively. Canadian Rheumatology Association guidelines recommend a target of remission or LDA within 3 to 6 months [1]. In the current study, the total proportions of patients who achieved DAS28 LDA or remission after 6 months were 69.2% in the monotherapy group and 56.1% in the combination therapy group; for SDAI, the proportions were 62.1 and 39.5%, and for CDAI the proportions were 51.0 and 37.5%, respectively. Assessment of CDAI does not include measurement of CRP or ESR, suggesting that effectiveness was not entirely dependent on normalization of acute phase reactants by tocilizumab. Effectiveness observed in the current study with tocilizumab monotherapy and combination therapy supports results from previous clinical trials [13] and studies in clinical practice [16, 17].

Effectiveness responses in patients naive to biological therapy and patients whose biological therapy failed indicate that substantial proportions of patients who had not responded to previous biological therapy were able to achieve high hurdle responses with tocilizumab treatment: 57.3% of biological-IR patients achieved DAS28 LDA or remission, 43.5% achieved SDAI LDA or remission, and 40.0% achieved CDAI LDA or remission after 6 months of tocilizumab treatment. In the open-label study of tocilizumab resembling clinical practice [22], rates of LDA and remission according to DAS28, SDAI, and CDAI after 6 months of tocilizumab treatment were higher in TNFi-naive patients (75.4, 68.5, and 65.0%, respectively) than in those who previously received TNFi treatment (61.0, 50.6, and 47.1%, respectively). Similarly, in a pooled analysis of long-term data from the tocilizumab phase 3-4 clinical trial program, rates of remission according to DAS28, SDAI, and ACR/EULAR Boolean criteria were lower in

TNF-IR patients than in DMARD-IR patients [24].

Patients who experienced secondary failure (discontinuing tocilizumab treatment because of loss of efficacy between months 6 and 12) tended to have more advanced disease and worse PROs than patients who experienced primary failure.

Medication adjustments occurred infrequently during the study, and 94.5% of patients were receiving stable doses of tocilizumab after 12 months. No new safety signals were identified for tocilizumab in this study; SAE and serious infection rates were consistent with those of the tocilizumab phase 3 clinical trial program and long-term extensions at 15.5/100 PY and 4.4/100 PY, respectively, during 12 months of tocilizumab treatment [24].

A limitation of this study was that tocilizumab dose de-escalation was not mandated for responders in the ACT-UP CARE study; future studies should investigate the effect of de-escalation from 8 to 4 mg/kg in patients who achieve remission or LDA. Another limitation is the post hoc nature of the analysis of primary and secondary failure. The subcutaneous formulation of tocilizumab was not approved in Canada when this study was conducted, and future studies should examine the effectiveness of subcutaneous tocilizumab in an observational setting now that it is approved in Canada [18]. Although this study is limited to a single Canadian cohort, it is part of a wider published global study that informs on the generalizability of the findings. In conclusion, treatment with tocilizumab was effective as monotherapy and in combination with csDMARDs in this real-world observational study of RA patients in routine clinical practice in Canada.

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Compliance with Ethics Guidelines. Enrolled patients provided written informed consent approved by the institutional review boards or independent ethics committees.

Data Availability. The data that support the findings of this study are available from the corresponding author on reasonable request and with permission from Hoffmann-La Roche Ltd.

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