Biologics initiation in moderate *versus* severe rheumatoid arthritis: real-world experience from a Canadian registry

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Abstract

Objective

To evaluate the treat-to-target experience, and quality of life measures of moderate and severe rheumatoid arthritis (RA) patients initiating a biologic in a real-world setting of a publicly funded payer system.

Methods

Biologic naive RA patients who had initiated their first biologic while enrolled in the Ontario Best Practices Research Initiative registry from 2008 to 2020 were selected if they had moderate (DAS28 >3.2 to ≤5.1) or severe (DAS28 >5.1) RA. Remission, LDA, DAS28, HAQ-DI, fatigue, sleep, drug persistence and characteristics associated with remission were assessed at 12 months post biologic initiation.

Results

Overall, 838 patients initiated their first biologic, 264 had moderate RA and 219 had severe RA. After 12 months, 44% moderate RA vs. 21% severe RA achieved remission ($p<0.0001$), and 59% moderate RA vs. 35% severe RA reached LDA ($p<0.0001$). Mean change (SD) from baseline in DAS28 was 2.2 (1.5) in severe RA vs. 1.4 (1.3) in moderate RA ($p<0.0001$), in fatigue score was 1.11 (3.2) in severe RA vs. 0.98 (3.2) in moderate RA ($p<0.0001$). Moderate disease at a biologic initiation was positively associated with remission ($p=0.0016$). Female gender ($p=0.0170$), and a higher HAQ-DI score at baseline ($p=0.0042$) were negatively associated with remission. Biologic persistence was 77% for moderate, and 73% for severe ($p=0.2444$).

Conclusion

Severe RA patients had higher mean score improvements in DAS28, sleep and fatigue. Moderate RA was more likely to reach remission or LDA. Both groups had similar biologic persistence at 12 months. These findings highlight the importance of the treat-to-target approach and its potential underutilisation in the real-world setting.

Key words

rheumatoid arthritis, biological therapies, disease activity score, quality of life, biologic persistence

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by persistent systemic inflammation, affecting 1% of the adult population. Historically, RA has been treated mainly with non-steroidal anti-inflammatory drugs for symptom reduction, and conventional disease-modifying anti-rheumatic drugs (csDMARDs) (1, 2). Since the 1990s, the introduction of biologics has revolutionised RA treatment. Three decades later, biologics are routinely recommended in the treat-to-target approach that aims for remission or low disease activity (LDA) in patients with RA (3, 4). The moderate and severe disease activity RA populations encompass a heterogenic group with a wide range in disease activity (5). However, there is limited evidence comparing the experience between the two groups following biologic initiation.

Prior studies have shown that more patients in the real-world setting have moderate disease activity, compared to randomised clinical trial (RCT) patients who tend to have more severe disease activity (6, 7). One study found that patients from observational studies had on average a 28-joint disease activity score (DAS28) of 0.6 points lower than patients enrolled in RCTs (5). This difference may affect the external validity and generalisability of some RCT results to real-world clinical practice (5, 6, 8, 9). Some other studies also suggested the treat-to-target approach is suboptimally implemented in clinical practice (9,10). We aimed to comprehensively evaluate the experience of moderate and severe RA patients initiating a biologic in the real-world setting of a publicly funded payer system.

This study used data over a 12-year period, from a Canadian registry, to compare real-world treatment patterns and outcomes in moderate and severe RA patients. The study aims to compare the proportion of patients with moderate and severe disease activity achieving remission, LDA, and a significant clinical DAS28 response at 12 months post initiation of their first biologic, as well as the improvements in Health Assessment Questionnaire Disability Index (HAQ-DI), fatigue and sleep scores between the two groups at 12 months. Additionally, the study aims to investigate biologic persistence during the 12 months of follow-up and identify baseline characteristics associated with biologic response.

Methods

Study design

The Ontario Best Practice Research Initiative (OBRI) is a multi-center provincial registry in Canada that prospectively collects data on RA patients followed in routine care. It incorporates rheumatologist assessments from approximately one-third of the rheumatologists in the province of Ontario. Patients are eligible for inclusion in the registry if they have a rheumatologist confirmed diagnosis of RA, disease onset ≥16 years of age, ≥18 years of age at registry enrolment, and ≥1 swollen joint. Treating rheumatologists collect data through patient assessment as per routine care, while patients also directly provide data via telephone interviews occurring every six months. The OBRI registry was established in accordance with the Declaration of Helsinki. Ethics approval was obtained for institutional sites and approval at each participating site (OBRI REB#: 07-0729 AE). Written informed consent was provided by all patients prior to enrolment in the registry. The data used for this analysis has been collected over 12 years. Also, the authors are not the legal owners of this data. The data was collected under the auspices of University Health Network (an academic hospital); therefore, the authors are not the custodians of this data. The data is protected by UHN Research Ethics Board and their authorisation is required for any use of this data.

Study population

Patients enrolled in the OBRI registry between January 2008 and January 2020 were selected for inclusion in the study if they had never been treated with a biologic, initiated their first biologic after enrolment, had a rheumatologist assessment within 30 days and a patient telephone interview within 60 days before or after initiating their first biologic, and a follow-up

at 12 months after biologic initiation. Patients were further selected for inclusion if their DAS28 at the time of biologic initiation was moderate or severe. Disease activity was defined according to the 2015 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria, DAS28 >3.2 to ≤5.1 for moderate, and DAS28 >5.1 for severe (11,12).

Study endpoints

Disease activity was calculated using DAS28. Disease remission was defined as DAS28 ≤2.6, and LDA as DAS28 ≤3.2. A minimum clinically important improvement in DAS28 was defined as a DAS28 change from baseline of ≥1.2 (13). Functional assessment was evaluated using patient completed HAQ-DI (0-3). The minimum clinically important difference for HAQ was defined as an improvement of ≥0.22 (14). Fatigue and sleep scores were assessed on a 10-point scale with 0 indicating no problem in the past week, and 10 indicating major problem in the past week. Fatigue and sleep scores were collected by patient interviews as part of the patient reported outcomes.

Statistical analysis

Baseline characteristics were summarised using descriptive statistics, which included mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical data. Comparisons of baseline characteristics and crude changes at 12 months were made between moderate and severe disease groups using the student's t-test for continuous variables, and the chi-square test for categorical variables. To test for selection bias, baseline characteristics were compared between included patients who had baseline DAS28 and excluded patients without baseline DAS28. Similarly, baseline characteristics were compared between included patients who had DAS28 at 12 months and excluded patients without DAS28 at 12 months.

Univariable logistic regression analyses were conducted to test the association between each of the following patient characteristics and remission at 12 months. The variables included were: age, gender, sociodemographic, DAS28 as moderate or severe at baseline, HAQ-DI, and number of comorbidities. Variables were included in the multivariable logistic regression models of remission if $p<0.2$ in the univariable analysis. To avoid multicollinearity, variables were also selected for variance inflation factor (VIF) <2.8. The results were presented as odds ratios (ORs). We used a multiple imputation technique to impute missing data by the Fully Conditional Specification (FCS) methods to test the robustness of the multivariable analysis results, sensitivity analysis was used to confirm the association between baseline variables selected and remission at 12 months, in a sub-cohort of patients who remained on the biologic and completed a 12-month follow-up visit.

Kaplan-Meier survival analysis was also used to graph the survival curve for persistence rates during the 12 months follow-up.

All tests were two-sided using the sig-

Table I. Clinical and demographics data at time of biologic initiation.

	Moderate-RA (DAS28 3.2-5.1) (n=264)	Severe-RA (DAS28 >5.1) (n=219)	*p*-value
Sociodemographics			
Age (years), mean (SD)	55.7 (13.1)	58.4 (12.3)	**0.0217**
Female, n (%)	211 (80)	177 (81)	0.8048
Education: college/university, n (%)	163 (63)	105 (50)	**0.0029**
Ever smoked[a], n (%)	111 (47)	105 (56)	0.0808
RA family history, n (%)	64 (24)	72 (33)	**0.0205**
Employed full/part time[b], n (%)	127 (51)	81 (40)	**0.0204**
Private Insurance, n (%)	165 (70)	111 (59)	**0.0163**
Academic rheumatologist, n (%)	76 (29)	67 (31)	0.6652
Disease characteristics			
RA disease duration (years), mean (SD)	7.1 (8.1)	6.8 (7.6)	0.6525
Early RA (duration ≤1 year), n (%)	52 (20)	49 (22)	0.4713
Ever presence of erosion[c], n (%)	122 (46)	93 (42)	0.4095
Rheumatoid factor positive[d], n (%)	174 (71)	153 (75)	0.3554
DAS28, mean (SD)	4.1 (0.5)	6.0 (0.6)	**<0.0001**
Swollen joint count (0-28), mean (SD)	5.4 (3.8)	8.8 (4.6)	**<0.0001**
Tender joint count (0-28), mean (SD)	4.6 (3.6)	12.2 (5.7)	**<0.0001**
Physician Global (0-10), mean (SD)	4.4 (2.0)	6.2 (1.9)	**<0.0001**
Patient Global (0-10), mean (SD)	5.3 (2.7)	6.4 (2.4)	**<0.0001**
Number of co-morbidities, median (IQ)	1.7 (1.8)	2.2 (2.1)	**0.0063**
ESR[e], mm/h, mean (SD)	18.6 (15.7)	35.0 (22.4)	**<0.0001**
CRP[f], mg/L, mean (SD)	8.5 (14.6)	16.4 (24.2)	**<0.0001**
Anti-CCP[g], n (%)	66 (58)	47 (57)	0.8031
HAQ disability index (0-3), mean (SD)	1.18 (0.72)	1.54 (0.71)	**<0.0001**
HAQ pain (0-3), mean (SD)	1.56 (0.81)	1.90 (0.77)	**<0.0001**
Concomitant oral steroid, n (%)	40 (15)	39 (18)	0.4452
Concomitant MTX, n (%)	166 (63)	153 (70)	0.1234
Fatigue (0-10), mean (SD)	5.3 (3.0)	6.1 (2.8)	**0.0043**
Sleep (0-10), mean (SD)	4.2 (3.2)	5.1 (3.4)	**0.0053**
Biologic drug			
Abatacept (Orencia), n (%)	6 (2)	9 (4)	
Adalimumab (Humira), n (%)	63 (24)	46 (21)	
Certolizumab (Cimzia), n (%)	37 (14)	25 (11)	
Etanercept (Enbrel), n (%)	102 (39)	87 (40)	0.5991*
Golimumab (Simponi), n (%)	30 (11)	27 (12)	
Infliximab (Remicade), n (%)	10 (4)	13 (6)	
Rituximab (Rituxan), n (%)	8 (3)	9 (4)	
Tocilizumab (Actemra), n (%)	8 (3)	3 (1)	

RA: rheumatoid arthritis; DAS28: 28-Joint Disease Activity Score; ESR: erythrocyte sedimentation rate (in millimetre per first hour); CRP: C-reactive protein (in milligrams per litre); anti-CCP anti-cyclic citrullinated peptide antibody; HAQ: Health Assessment Questionnaire; DMARDs: disease-modifying anti-rheumatic drugs; MTX: methotrexate

*p-value=0.5991 is for all biologic drugs between the moderate and severe groups.

[a]n=50 missing data for number of patients who ever smoked. [b]n=18 missing for employment full/part time. [c]n=34 missing for erosion. [d]n=28 missing for RF positive. [e]n=24 missing for ESR. [f]n=36 missing for CRP. [g]n=290 missing for Anti-CPP.

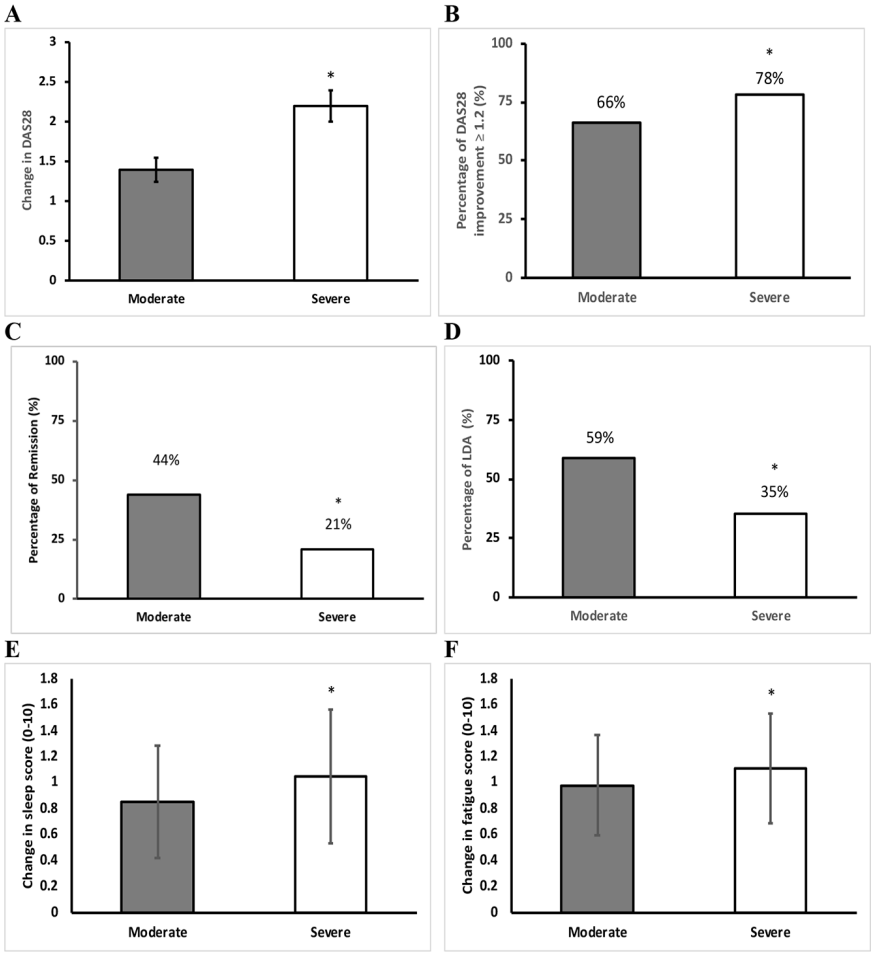

Fig. 1. Change in disease activity and functional status at 12 months post initiation of first biologic. *p<0.001.

nificance level of 0.05. All analyses were performed using SAS v. 9.4 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

Overall, 838 RA patients initiated their first biologic while enrolled in OBRI between Jan 17th, 2008 and Jan 1st, 2020, of whom 483 patients had moderate or severe disease activity and had follow-up data for at least 12 months. For these 483 patients, 264 had moderate disease activity (55%) and 219 patients had severe disease activity (45%) (Supplementary Fig. S1).

Baseline sociodemographic and disease characteristics were assessed and compared between the moderate and severe groups (Table I). The mean age in the severe group was higher than in the moderate group (58.4 *vs*. 55.7 years, p=0.0217). Family history of RA was reported more often in the severe group (33% *vs*. 24%, p=0.0205). The percentage of females in each group was similar, 80% in moderate, and 81% in severe (p=0.8048). Both groups also had similar percentages of patients seen by a rheumatologist in an academic centre, 29% in moderate *versus* 31% in severe (p=0.6652). As expected, severe patients had significantly higher mean DAS28 (SD) (6.0 (0.6) *vs*. 4.1 (0.5), swollen joint count (SJC), tender joint count (TJC), physician global, patient global, ESR, CRP, HAQ-DI, HAQ-pain, fatigue, and sleep values. Moderate and severe groups had similar duration of RA, and similar percentages of patients on concomitant methotrexate treatment.

Selection bias was explored by comparing the characteristics of included and excluded patients. There was no significant difference in baseline characteristics between patients who had baseline DAS28 and the excluded patients without baseline DAS28 (Suppl. Table S1). Similarly, the baseline characteristics between patients who had DAS28 at 12 months and the excluded patients without DAS28 at 12 months were similar (Suppl. Table S2).

Clinical outcomes in patients with moderate and severe disease activity

After 12 months following biologic initiation, the percentage of patients achieving remission in the moderate group was 44%, compared to 21% in the severe group (p<0.0001). Similarly, the percentage of patients reaching LDA at 12 months was higher in the moderate group compared to the severe group (59% *vs*. 35%, p<0.0001). The mean DAS28 (SD) at 12 months for the moderate group was 2.75 (1.28), and for the severe group 3.76 (1.44). The mean change (SD) from baseline in DAS28 was 1.4 (1.3) in the moderate group *versus* 2.2 (1.5) in the severe group (p<0.0001). The percentage of patients achieving a minimum clinically important improvement in DAS28 was 66% in the moderate group *versus* 78% in the severe group (p=0.0049) (Fig. 1 and Suppl. Table S3).

At the 12-month follow-up, the mean HAQ (SD) for the moderate group was 0.89 (0.75), and for the severe group 1.21 (0.84). The percentage of patients achieving a minimum clinically important improvement in HAQ-DI was similar between moderate and severe disease activity patients. For other quality of life measures, the mean (SD) change in fatigue at 12 months was 1.11 (3.2) in the severe group compared to 0.98 (3.2) in the moderate group (p<0.0001), and the mean (SD) change in sleep score was 1.05 (3.9) in the severe group *versus* 0.85 (3.6) in the moderate group (p=0.004) (Fig. 1 and Suppl. Table S3).

Characteristics associated with remission

Characteristics associated with DAS28 remission at 12 months were assessed using multivariable logistic regression analysis (Table II). Moderate disease at the time of biologic initiation was positively associated with remission (odds ratio (OR) 2.61, 95% confidence inter-

val (CI) 1.44-4.73; p=0.0016). In contrast, factors that were negatively associated with remission included female gender (OR 0.45, 95% CI 0.24–0.87; p=0.0170), and a higher HAQ-DI score at baseline (OR 0.51, 95% CI 0.33–0.81; p=0.0042). Findings from the sensitivity analysis by multiple imputation technique (FCS) methods showed similar results (Suppl. Table S4).

Sensitivity analyses were also completed using 368 patients who remained on the biologic for 12 months, and who had physician and patient reported assessments at 12 months. The sensitivity analyses confirmed the same findings as the multivariable logistic regression model (Suppl. Table S5).

Biologic persistence

Biologic persistence was evaluated using the Kaplan-Meier survival curve. After 12 months, the cumulative probability of remaining on treatment with the first biologic was 77% for the moderate group, and 73% for the severe group, shown in Figure 2. However, there was no significant difference between the two Kaplan-Meier curves (p=0.2444). 6% of moderate disease patients, and 10% of severe disease patients switched biologics during the 12-month follow-up.

The top three reasons for discontinuation were primary failure, adverse effect, and secondary failure, respectively. Primary failure was defined as no clinical response observed within 3 months, while secondary failure was defined as failure to maintain response after 3 months (15). Additional detailed reasons for discontinuation can be found in Supplementary Table S6.

Discussion

This retrospective observational cohort study aimed to investigate the real-world experience of moderate and severe RA patients who initiated their first biologic as part of their routine clinical care. The study found that at 12 months following biologic initiation, RA patients with moderate disease activity were more likely to reach target states, defined as remission or low disease activity. Severe disease activity patients had higher mean score improvements in

Table II. Characteristics associated with RA remission at 12 months*.

	Univariate analysis OR (95% CI), p-value (n=466)	Multivariate analysis OR (95% CI), p-value (n=466)
Sociodemographic		
Age (years)	**0.98 (0.96-0.99), 0.0030**	0.99 (0.96-1.01), 0.2496
Female gender	**0.44 (0.28-0.70), 0.0006**	**0.45 (0.24-0.87), 0.0170**
Education status		
High school or less	Ref	—
Post-secondary	1.33 (0.89-1.98), 0.1593	0.98 (0.57-1.69), 0.9322
Ever smoked		
No	Ref	—
Yes	1.02 (0.68-1.54), 0.9196	
RA family history		
No	Ref	
Yes	0.71 (0.45-1.12), 0.1389	0.93 (0.52-1.66), 0.8025
Employment status		
None	Ref	
Full or Part time	**1.53 (1.03-2.28), 0.0358**	0.67 (0.36-1.27), 0.2196
Private Insurance		
No	Ref	
Yes	1.57 (1.01-2.45), 0.0445	1.41 (0.77-2.59), 0.2678
Disease characteristics		
DAS28 groups (moderate vs severe)	**2.84 (1.88-4.29), <0.0001**	**2.61 (1.44-4.73), 0.0016**
RA disease duration (years)	0.98 (0.96-1.01), 0.1803	1.00 (0.96-1.03), 0.8915
Physician global	**0.90 (0.82-0.99), 0.0356**	1.01 (0.87-1.17), 0.8946
HAQ-DI	**0.41 (0.30-0.56), <0.0001**	**0.51 (0.33-0.81), 0.0042**
HAQ pain	**0.65 (0.50-0.84), 0.0011**	—
Morning stiffness (0-10)	**0.93 (0.87-0.995), 0.0349**	1.03 (0.93-1.13), 0.6084
Fatigue (0-10)	**0.88 (0.82-0.94), 0.0003**	0.96 (0.87-1.06), 0.3916
Sleep (0-10)	**0.88 (0.83-0.94), <0.0001**	—
Number of comorbidities	**0.88 (0.80-0.98), 0.0202**	0.93 (0.81-1.07), 0.3123
Physician information		
Physician academic position		
Community-based	Ref	
Academic-based	0.70 (0.45-1.08), 0.1070	0.62 (0.34-1.11), 0.1067

*patients who have DAS28 at baseline and 12 month DAS28 (n=466) including moderate disease group (n=255) and severe disease group (n=211).

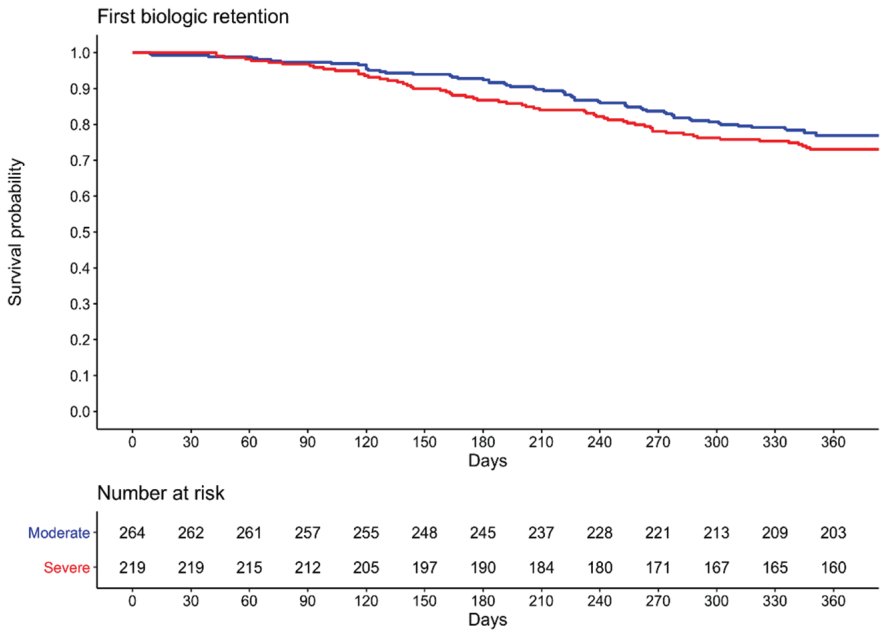

Fig. 2. Drug persistence between moderate and severe patients over 12 months after initiating the first biologic (p=0.2444).

DAS28, HAQ-DI, sleep and fatigue at 12 months when compared with moderate patients. Moderate disease was also positively associated with remission at 12 months, whereas female sex and a higher HAQ-DI score at baseline were negatively associated with remission. At baseline, severe patients had significantly higher mean DAS28 (SD) compared to moderate patients (6.0 (0.6) *vs*. 4.1 (0.5). The baseline DAS28 in our population is consistent with those in other real-world studies (13).

Approximately 23% more patients reached target states of remission and LDA at 12 months post biologic initiation in the moderate group compared to the severe group. These results support the idea that the treat-to-target approach may be easier to attain before the disease has progressed to higher levels of disease activity. Our results are consistent with results from RA registries in other countries, although these other studies often focused on a specific biologic drug rather than biologics as a class (16, 17). For example, a study from the Italian GISEA register compared moderate *versus* severe patients on etanercept and found that DAS28 remission was easier to achieve in moderate compared to severe patients, with 47.9% achieving remission compared to 24.5% at 12 months (13).

We wish to note that 105 patients in the OBRI registry started a biologic while in LDA or remission during the 12-year study period. We found that the tender joints mean is 1.8 (±3.0), swollen joints mean is 3.3 (±3.3), and the physician global is 2.8 (±2.1) in these patients. We evaluated the physician global because this score is not used in the DAS28 score calculations. The physicians in our cohort likely decided to start a biologic in these patients based on their own judgement because of the observed active tender and swollen joints at baseline. It is also interesting to note that the majority of patients who reached LDA and remission did so within 6 months (Suppl. Table S3). Although our primary goal was not to compare the percentage of patients reaching remission and LDA at 6 months *versus* 12 months, we conducted this comparison as exploratory work. Our finding provides real-world evidence to support EULAR guideline recommendations to switch therapy if target states are not reached in the first 6 months of biologic initiation (12, 18).

However, in our real-world cohort, a biologic switch did not always occur when target states were not reached. At 12 months after biologic initiation, roughly 77% of patients in the moderate group remained on the same biologic, compared to 73% in the severe group, albeit the difference was not statistically significant. Discontinuation reasons are listed in Supplementary Table S6. Only 6% of moderate disease patients, and 10% of severe disease patients switched biologics during the 12 months follow-up. The persistence and switch rates were similar to those reported by other real-world studies (19, 20). A US registry study with a similar percentage of patients reaching LDA at the end of 1 year following biologic initiation, found biologic discontinuation occurred in less than 20% of patients, and biologic switch occurred in only 10% of patients (20). The low discontinuation rate may be attributed to patients and physicians willing to accept a clinically significant improvement in outcome even if aggressive targets have not been achieved. Our study confirms the findings of other studies that the treat-to-target approach may be underutilised in clinical practice (21). Other studies have also proposed the cost and inconvenience of switching a biologic may often be the barriers (22). However, patients who met the public funding criteria to initiate a biologic in Ontario Canada would also qualify for biologic switches. This suggests that factors other than cost in our cohort may more likely contribute to low biologic switch rates. In the real-world setting, the follow-up appointments may occur later than intended, due to capacity constraints of the clinics and staff shortages, resulting in delayed assessment and therapy switch. Further research is needed to assess barriers and reasons for not switching biologics when treat-to-target endpoints were not met. These findings highlight the importance of the treat-to-target approach and its potential underutilisation in the real-world setting. Targeted studies to better understand the decisions and any factors limiting biologic switches in the real-world setting are needed.

Studies have suggested that quality of life measures contribute more to patients' perception of their disease activity than numerical disease activity scores (23-25). To our knowledge, our study is the first to compare changes in sleep and fatigue scores upon initiation of a biologic in patients with moderate and severe RA. Both disease groups experienced improvement in sleep and fatigue scores, with the severe group having a higher reduction in both scores than the moderate group. This aligns with our prior finding that severe patients tend to have better improvement in mean disease measurement scores when compared to moderate patients. Many studies have shown that quality of life endpoints carry considerable weight in RA patients' perception of treatment success (23, 26, 27). Our results highlight the importance of biologics in helping to reduce the substantial humanistic burden in both the moderate and severe RA population.

Moderate disease activity at baseline was positively associated with remission. We found female gender and a higher HAQ-DI baseline score to be negatively associated with remission. Factors associated with remission generally aligned with previous studies (28-30). Though some other studies have concluded slightly different factors associated with remission (4, 13). This might be attributed to the fact that registries enrol patients in different countries, therefore, unaccounted differences may exist in each study population. It is interesting to note that in our study, whether patients were seen by a rheumatologist at an academic centre *versus* community practice, whether patients had private insurance, or whether patients were employed were not positively or negatively associated with remission. This could be attributed to the standardised treatment and funding models in Ontario, Canada.

In an exploratory analysis, we compared the baseline characteristics of the individual biologics. For tumor necro-

sis factor (TNF) inhibitors, the individual drugs included are adalimumab, certolizumab, etanercept, golimumab and infliximab. The non-TNF inhibitors are grouped together due to the smaller number of patients on each drug. The non-TNF inhibitors included are abatacept, rituximab and tocilizumab. Most baseline characteristics were consistent across individual drugs (Suppl. Table S7). Additionally, we assessed the proportion of patients reaching remission and LDA across individual biologics at 12 months after initiating the first biologic. We found that more moderate disease patients reached remission and LDA at 12 months across all drugs when compared with severe disease patients. On an individual drug level, patients who started certolizumab had the highest percentage reaching remission at 12 months (Suppl. Table S8). Patients who started on golimumab had the highest percentage reaching LDA at 12 months (Suppl. Table S9). However, due to the small sample size, the results need to be interpreted with caution.

Limitations specific to observational studies need to be considered. Although our statistical model adjusted for potential confounders, we cannot rule out the effects of unmeasured and unpredictable confounding factors. Patients lost to follow-up may also have influenced results. 15% of moderate patients, and 6% of severe patients did not have follow-up data at 12 months. However, this is within the general rule that accepts a loss to follow-up rate of under 20% of the sample for observational studies (31). Remission and LDA were defined using the DAS28 criteria, which can be more lenient than other definitions (25). Finally, the experiences of the patient population in Ontario, Canada, which have access to publicly funded biologics, may not be reflective of patients in different funding systems.

In conclusion, the study found that at 12 months after initiating the first biologic, RA patients with severe disease activity had higher mean score improvements in DAS28, sleep and fatigue, whereas RA patients with moderate disease activity were more likely to reach treat-to-target states (remission and LDA). The study also found that moderate disease was positively associated with remission when compared to severe disease and female gender and higher HAQ-DI score at baseline were negatively associated with remission. Lastly, both moderate and severe groups had similar biologic persistence with the first biologic at 12 months. These findings highlight the importance of the treat-to-target approach in the real-world setting.

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