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ORIGINAL ARTICLE

Predictors of patient decision to discontinue anti-rheumatic medication in patients with rheumatoid arthritis: results from the Ontario best practices research initiative

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Abstract Despite the availability of treatment guidelines and effective treatments, real-world effectiveness remains suboptimal partly due to poor patient medication adherence. We evaluated a comprehensive set of sociodemographic, health insurance, and disease-related factors for association with patient decision to discontinue anti-rheumatic medications (ARMs) in a large observational RA cohort in Ontario, Canada. Patients from the Ontario Best Practices Research Initiative registry were included. The following predictors of ARM discontinuation were evaluated with cox-regression: patient age, gender, education, income, smoking, health insurance type/coverage, RA duration, erosion presence, RF positivity, DAS28-ESR, physician global, HAQ-DI, comorbidity number, ARM types, and physician characteristics (gender, academic position, urban vs. rural, distance from patient's residence). Patients (1762) were included with a mean (SD) age of 57.4 years (13.0). Approximately 80% were female, 29% had early (≤ 1 year) RA, and 70% were RF-positive. Mean (SD) baseline DAS28-ESR and HAQ-DI were 4.5 (1.5) and 1.2 (0.76), respectively. In multivariate analysis, married status (HR [95%CI] 0.73 [0.56–0.96]), RF positivity (0.73 [0.56–0.96]), and higher comorbidity number (0.92 [0.85–0.99]) were significant predictors of ARMs continuation while higher physician global (1.10 [1.04–1.15]), NSAID use (1.75 [1.29–2.38]), and number of ARMs (1.23 [1.07–1.40]) were associated with ARMs discontinuation. In a subset analysis assessing conventional or biologic DMARD discontinuation, higher HAQ-DI and biologic use over time were associated with lower hazard for discontinuation. Several sociodemographic, disease, and treatment parameters were identified as independent predictors of patient discontinuation of ARMs. These results should be considered when developing patient adherence support programs and in the choice of treatment regimens.

Keywords Adherence · Anti-rheumatic medication · DMARDs · Registry · Rheumatoid arthritis · Treatment discontinuation

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Introduction

Despite the availability of highly effective treatments, a disconnect exists between the efficacy shown in controlled clinical trials and the real-world effectiveness observed in routine clinical care. Suboptimal adherence to treatment has been recognized as the most important patient-centric modifiable factor affecting the effectiveness of approved treatments for chronic conditions including rheumatoid arthritis (RA) [1]. Previous studies have shown that non-adherence to anti-rheumatic medications (ARMs) is associated with higher disease activity and disability, disease flares, increased healthcare resource

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utilization, and associated cost [2–6]. In addition, undisclosed non-adherence is often perceived as non-response to treatment and associated with higher treatment doses or switching therapies which, in addition to further increasing the health care cost, puts patients at higher risk for drug side effects or delays to responses [7].

The rate of non-adherence to ARMs in RA patients has been shown to be highly variable, ranging from 30 to 80% [8, 9]. Furthermore, inconsistent results have been previously reported in the literature in regard to factors predicting adherence to ARMs [8, 10–12]. This variability in both the rate and predictors of non-adherence is largely due to the use of different definitions of non-adherence, the use of different instruments for assessing adherence, the evaluations of different sets of potential predictors, and the different study designs used in each study [9, 13–18]. Another important consideration in assessing determinants of patient non-adherence with treatment is regional variability due to different cultural influences, practice patterns, and local reimbursement policies affecting access to care, which necessitates country-specific evaluations.

Thus, in order to describe the rate of patient decision to discontinue ARMs in Ontario, Canada, as well as to identify determinants of ARMs discontinuation, we investigated a comprehensive set of sociodemographic, disease, treatment, and physician practice parameters longitudinally collected in the Ontario Best Practices Research (OBRI).

Material and methods

Data source and patients

The OBRI is a multicenter registry across Ontario, Canada, collecting data from both physicians and patients with RA followed under routine care. It incorporates physician assessments and a unique method of collecting data from the patients directly using telephone interviewers. All patients have a physician-confirmed diagnosis of RA, are 18 years or older at enrollment into the registry, and have had disease onset after 16 years of age. Between January 2008 and Jan 2015, 2591 eligible patients across 57 sites gave their consent to participate in physician evaluations, and 2545 agreed to patient interviews. Institutional research ethics approval was obtained prior to recruitment.

For this study, we restricted our population to patients who consented to participate in both patient interviews and physician evaluations, with at least 2 years of follow-up. To obtain the most accurate information for start and stop dates of ARMs from patient interviews, we excluded patients with a gap of 60 days or more between patient enrolment to the registry and their first interview (Fig. 1). A total of 1762 RA patients who were on at least 1 ARM at OBRI enrolment were included and followed until the first patient's decision to discontinue ARM or the last available visit while on treatment.

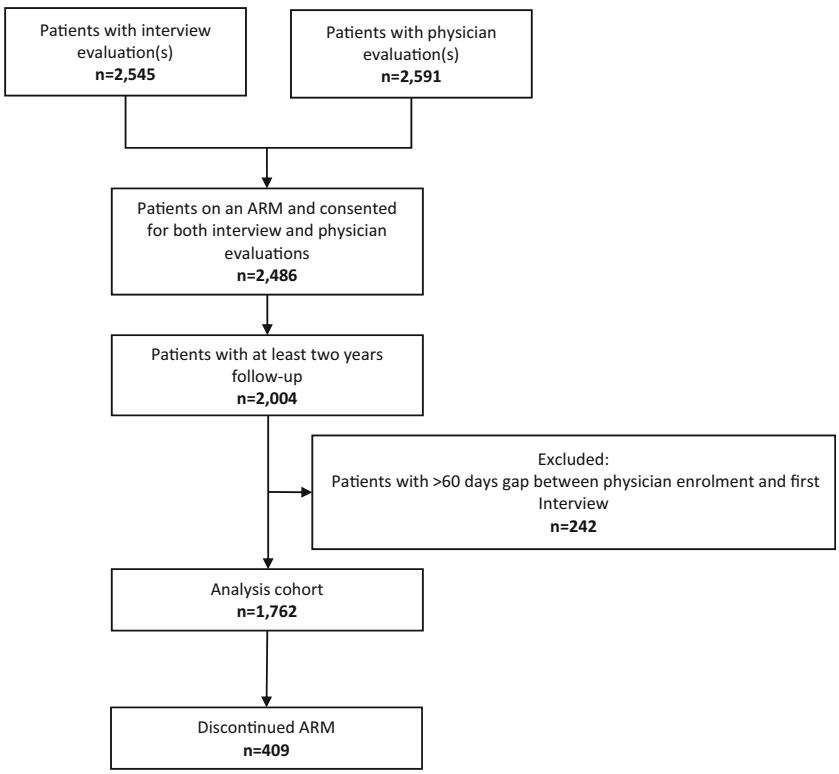

Fig. 1 Patient flowchart

Using an interview questionnaire, at each interview, patients are asked if they have stopped taking any ARMs and, if so, to provide the reason for ARMs discontinuation. The following reasons for ARMs discontinuation are collected: (1) disease improvement, (2) treatment completion, (3) doctor's decision, (4) patient's decision, (5) adverse event/side effect, (6) primary failure (never achieving a response), (7) secondary failure (failure to maintain response after 3 months of treatment), (8) loss of coverage/lack of funding, (9) pregnancy, and (10) other. For this analysis, non-adherence to ARMs was defined as discontinuation due to patient's decision (no. 4).

Statistical analysis

The following core set of sociodemographic, treatment, physician, and disease parameters were assessed: (1) time-fixed variables at enrolment: age, gender, residential area (urban vs. rural), distance between residential address and clinical site, marital status, physician gender, physician academic position, disease duration, rheumatoid factor (RF) status, prior use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), prior use of biologic DMARDs (bDMARDs); (2) time-dependent variables: smoking status, annual household income, type of health insurance, % prescriptions covered by insurer, Disease Activity Score in 28 joints (DAS28-ESR), physician global score, Health Assessment Questionnaire disability index (HAQ-DI), use of csDMARDs, bDMARDs, steroids, non-steroid anti-inflammatory drugs (NSAIDs), number of ARMs, and number of chronic comorbidities. Baseline characteristics were described using the mean and standard deviation (SD) for continuous variables or the count and proportion for categorical variables.

The primary analysis examined the association between the core set of variables and time to ARMs discontinuation due to patient's decision using univariate and multivariate Cox proportional hazards regression models. The proportional hazards assumption was tested for each model by inspecting the Schoenfeld residuals. Patients discontinuing their medication due to reasons other than patient's decision and those not discontinuing their medication were right censored at time of discontinuation and the latest visit, respectively. Variables with p value ≤ 0.20 in univariate analysis were included in a saturated multivariate analysis, and a backward stepwise regression model was then applied to select variables with p values ≤ 0.15 from the saturated multivariate model. In addition, a subset analysis was conducted using similar methods in order to identify independent predictors of csDMARD and/or bDMARD discontinuation due to patient's decision. All statistical analyses were performed using SAS 9.4 (Cary, NC; SAS Institute Inc.).

Results

Baseline characteristics and follow-up information

A total of 1762 RA patients were included in the analysis. Table 1 summarizes the patient and physician characteristics at the time of enrolment in the registry; for comparability evaluation, the baseline characteristics of the full OBRI RA cohort is also presented. The mean age (SD) of the analysis cohort was 57.4 years (13.0) and disease duration was 8.5 years (9.3). Approximately 80% were female, 29% had early ($\leq$ 1 year disease duration) RA, and 70% were RF positive. Mean (SD) DAS28-ESR and HAQ-DI at enrolment were 4.5 (1.5) and 1.2 (0.76), respectively.

During a mean (SD) follow-up of 1.3 years (1.5), 409 (23.2%) patients discontinued one or more ARMs due to their own decision including csDMARDs (n = 147; 8.3%), bDMARDs (n = 20; 1.1%), steroids (n = 43; 2.4%), NSAIDs (n = 98; 5.6%), and other ARMs (n = 101; 5.7%) (data not shown).

Predictors of non-adherence (patient's decision to discontinue ARM) (primary analysis)

Table 2 summarizes the results of the primary analysis assessing the association between various sociodemographic, treatment, physician and disease parameters, and patient non-adherence with ARMs. In univariate analysis, older age (hazard ratio [HR], 0.99; 95% CI, 0.98–0.99), married status (HR, 0.82; 95% CI, 0.67–1.00), and RF positivity (HR, 0.79; 95% CI, 0.64–0.99) were significantly (p value < 0.05) associated with lower hazard of non-adherence. In contrast, physician academic (or mixed) affiliation (HR, 1.24; 95% CI, 1.02–1.51), higher number of prior csDMARDs use at enrolment (HR, 1.08; 95% CI, 1.01–1.15), total number of ARMs (HR, 1.30; 95% CI, 1.19–1.43), increased DAS28-ESR (HR, 1.10; 95% CI, 1.02–1.18), physician global score (HR, 1.10; 95% CI, 1.05–1.15), use of steroids (HR, 1.26; 95% CI, 1.00–1.60), and use of NSAIDs (HR, 1.90; 95% CI, 1.54–2.34) over time were significantly (p value < 0.05) associated with increased hazard of non-adherence (Table 2).

In the multivariate analysis, married status (HR, 0.73; 95% CI, 0.56–0.96), RF positivity (HR, 0.73; 95% CI, 0.56–0.96), and increased number of comorbidities (HR, 0.92; 95% CI, 0.85–0.99) were significantly (p value < 0.05) associated with a lower hazard of non-adherence, whereas increased physician global score (HR, 1.10; 95% CI, 1.04–1.15), use of NSAIDs (HR, 1.75; 95% CI, 1.29–2.38), and increased total number of ARMs used over time (HR, 1.23; 95% CI, 1.07–1.40) were significantly associated with a higher hazard for non-adherence (Table 2).

Table 1 Baseline patient and physician characteristics and patient disease parameters

	Analysis cohort *N* = 1762	Total cohort *N* = 2486
Sociodemographics		
Age (years), mean (SD)	57.4 (13.0)	57.2 (12.8)
Female gender, *n* (%)	1369 (77.7)	1680 (67.6)
Marital status, *n* (%)		
Single/widowed/divorced	541 (30.7)	767 (30.9)
Married	1221 (69.3)	1719 (69.1)
Race, *n* (%)		
Caucasian (white)	1499 (85.1)	2118 (85.2)
Non-Caucasian	184 (10.4)	261 (10.5)
Missing	79 (4.5)	107 (4.3)
Spoken Language, *n* (%)		
English	1624 (92.2)	2287 (92.0)
Other languages	138 (7.8)	199 (8.0)
Education status, *n* (%)		
High school or less	785 (44.6)	1098 (44.2)
Post-secondary	975 (55.3)	1386 (55.8)
Missing	2 (0.1)	2 (0.1)
Annual income class, n (%)		
< $50,000	590 (33.5)	835 (33.6)
≥ $50,000	739 (41.9)	1066 (42.9)
Missing	433 (24.6)	585 (23.5)
Smoking history, *n* (%)		
Never smoked	804 (45.6)	1132 (45.5)
Former smoker	665 (37.7)	940 (37.8)
Current smoker	292 (16.6)	413 (16.6)
Missing	1 (0.1)	1 (0.1)
Health insurance information		
Health insurance, *n* (%)		
No private	529 (30.0)	544 (21.9)
Private	1184 (67.2)	1882 (75.7)
Missing	49 (2.8)	60 (2.4)
% prescriptions covered by health insurance, mean (SD)	80.6 (31.6)	80.8 (31.5)
Disease characteristics		
Disease duration (years.), mean (SD)	8.5 (9.3)	8.6 (9.8)
Early RA[a], *n* (%)		
No	1251 (71.0)	1749 (70.4)
Yes	511 (29.0)	737 (29.6)
Ever presence of erosion, *n* (%)		
No	643 (36.5)	957 (38.5)
Yes	961 (54.5)	1318 (53.0)
Missing	158 (9.0)	211 (8.5)
RF positive, *n* (%)		
No	417 (23.7)	488 (19.6)
Yes	1224 (69.5)	1513 (60.9)
Missing	121 (6.8)	485 (19.5)
Swollen joint count (0–28), mean (SD)	5.8 (5.1)	5.9 (5.0)
Tender joint count (0–28), mean (SD)	6.6 (6.3)	6.5 (6.4)
DAS28-ESR, mean (SD)	4.5 (1.5)	4.5 (1.5)

Table 1 (continued)

	Analysis cohort $N = 1762$	Total cohort $N = 2486$
Physician Global (1–10), mean (SD)	4.5 (2.4)	4.4 (2.4)
Patient Global (1–10), mean (SD)	4.9 (2.7)	4.9 (2.7)
HAQ disability index (0–3), mean (SD)	1.2 (0.76)	1.2 (0.80)
Medication information		
Prior use of bDMARDs, *n* (%)		
No	1274 (72.3)	1765 (71.0)
Yes	488 (27.7)	709 (28.5)
Number of prior bDMARDs, mean (SD)	1.7 (1.0)	0.5 (1.0)
Prior use of csDMARDs, *n* (%)		
No	250 (14.2)	406 (16.3)
Yes	1512 (85.8)	2067 (83.1)
Number of prior csDMARDs, mean (SD)	2.4 (1.2)	2.1 (1.4)
Physician information		
Female physician gender, *n* (%)	714 (40.5)	1017 (40.9)
Physician academic position, *n* (%)		
Community-based	838 (47.6)	1162 (46.7)
Academic or mixed based	924 (52.4)	1324 (53.3)
Residential address, *n* (%)		
Urban	1473 (83.6)	2050 (82.5)
Rural	289 (16.4)	421 (16.9)
Distance between patient residence and clinical site, *n* (%)		
≤ 25 km	785 (44.6)	785 (31.6)
> 25 km	917 (52.0)	917 (36.9)
Missing	60 (3.4)	784 (31.5)

[a] Disease duration ≤ 1 year

Predictors of non-adherence (patient's decision to discontinue DMARDs) (subset analysis)

Subset analysis explored predictors of discontinuation of csDMARDs and bDMARDs specifically, being the two most common ARMs ($N = 167$). Following variable selection, multivariate analysis showed that higher HAQ-DI over time (HR, 0.70; 95% CI, 0.50–0.97) and use of bDMARDs (HR, 0.50; 95% CI, 0.30–0.81) were significantly associated with a lower hazard for non-adherence with DMARDs (csDMARDs and/or bDMARDs) (Table 3).

Discussion

Using non-adherence defined as medication discontinuation due to patient's own decision, we have shown that the rate of non-adherence for all ARMs was 23% with a lower non-adherence rate for csDMARDs and/or bDMARDs (9.4%). This is consistent with the rate of non-adherence to DMARDs (9.3%) reported in a previous study which used a self-reported medication adherence scale [9].

Existing literature on predictors of ARMs non-adherence is inconsistent possibly due to the use of various definitions for non-adherence [8, 19]; the use of different instruments for assessing adherence; the evaluations of different, often limited, sets of potential predictors; the use of different study designs used (mostly cross-sectional and short-term prospective studies); and regional differences. In this longitudinal prospective study, we observed a statistically significant positive association of married status (as compared to single/widowed/divorced status), RF positivity, as well as higher number of comorbidities with adherence to prescribed ARMs. This is consistent with previous studies showing a positive association between positive RF and presence of comorbidity(ies) with adherence [16, 20–23]. The impact of marital status on ARM adherence may reflect differences in behavioral and psychological factors previously reported to affect adherence [15]. Similar to other previous studies, we also observed that patients with higher physician global scores and higher number of ARMs are more likely to discontinue an ARM [9, 13].

Table 2 Time to ARM discontinuation due to patient's decision

	HR (95% CI), *p* value		
	Univariate analysis[a] N_{Events} = 409	Multivariate saturated analysis[b] N_{Events} = 247	Backward stepwise regression analysis[c] N_{Events} = 247
Sociodemographics			
Age (years)	**0.99 (0.98–0.99), 0.03**	1.00 (0.99–1.01), 098	–
Female gender	1.09 (0.85–1.38), 0.50	–	–
Marital status			
Single/widowed/divorced	Ref	Ref	Ref
Married	**0.82 (0.67–1.00), 0.05**	**0.72 (0.55–0.95), 0.02**	**0.73 (0.56–0.96), 0.02**
Education status			
High school or less	Ref	Ref	–
Post-secondary	**1.20 (0.98–1.46), 0.07**	1.10 (0.85–1.43), 0.47	
Annual income class during follow-up			
< $50,000	Ref	–	–
≥ $50,000	1.10 (0.87–1.38), 0.43		
Smoking history during follow-up			
Never smoked	Ref		–
Former smoker	0.99 (0.80–1.23), 0.95	–	
Current smoker	0.96 (0.71–1.29), 0.80		
Health insurance information			
Health insurance		–	–
No private	Ref		
Private	1.08 (0.83–1.40), 0.58		
% prescriptions covered by health insurance		–	–
during follow-up	1.01 (1.00–1.02), 0.25		
Disease characteristics			
Disease duration at baseline (years)	0.99 (0.99–1.01), 0.70	–	–
Early RA			
No	Ref	–	–
Yes	1.04 (0.84–1.29), 0.70		
Ever presence of erosion			
No	Ref	–	–
Yes	0.96 (0.82–1.12), 0.57		
RF positive			
No	Ref	Ref	Ref
Yes	**0.79 (0.64–0.99), 0.04**	**0.74 (0.56–0.97), 0.03**	**0.73 (0.56–0.96), 0.02**
DAS28-ESR during follow-up	**1.10 (1.02–1.18), 0.02**	0.98 (0.87–1.11), 0.74	-
Physician global during follow-up	**1.10 (1.05–1.15), <0.0001**	**1.12 (1.04–1.20), 0.003**	**1.10 (1.04–1.15), 0.001**
HAQ-DI during follow-up	**1.09 (0.97–1.24), 0.15**	0.89 (0.74–1.08), 0.25	-
Number of comorbidities during follow-up	**0.96 (0.90–1.01), 0.11**	**0.94 (0.87–1.01), 0.11**	**0.92 (0.85–0.99), 0.02**
Medication information			
Prior csDMARDs use at baseline			
No	Ref	–	–
Yes	1.18 (0.89–1.57), 0.25		
Prior bDMARDs use at baseline			
No	Ref	–	–
Yes	1.04 (0.83–1.29), 0.75		
	1.08 (1.01–1.15), 0.03	1.03 (0.94–1.13), 0.57	–

Table 2 (continued)

	HR (95% CI), *p* value		
	Univariate analysis[a] N_{Events} = 409	Multivariate saturated analysis[b] N_{Events} = 247	Backward stepwise regression analysis[c] N_{Events} = 247
Number of prior csDMARDs at baseline			
Number of prior bDMARDs at baseline	1.04 (0.93–1.15), 0.50		–
csDMARDs use during follow-up			
No	Ref	–	–
Yes	1.12 (0.90–1.29), 0.31		
bDMARDs use during follow-up			
No	Ref	–	–
Yes	1.04 (0.84–1.29), 0.71		
Steroid use during follow-up			
No	Ref	Ref	–
Yes	**1.26 (1.00–1.60), 0.05**	1.04 (0.72–1.51), 0.83	
NSAIDs use during follow-up			
No	Ref	Ref	Ref
Yes	**1.90 (1.54–2.34), <0.0001**	**1.78 (1.28–2.48), 0.001**	**1.75 (1.29–2.38), 0.0003**
Total number of ARMs during follow-up	**1.30 (1.19–1.43), <0.0001**	**1.22 (1.03–1.44), 0.02**	**1.23 (1.07–1.40), 0.003**
Physician information			
Female physician gender	**1.21 (0.99–1.47), 0.06**	1.18 (0.90–1.53), 0.23	–
Physician academic position			
Community-based	Ref	Ref	–
Academic or mixed based	**1.24 (1.02–1.51), 0.03**	1.07 (0.82–1.39), 0.62	
Residential address			
Urban	Ref	–	–
Rural	1.13 (0.88–1.45), 0.33		
Distance between patient residence and clinical site			–
≤ 25 km	Ref	–	
> 25 km	1.13 (0.93–1.38), 0.22		

[a] *P* values ≤ 0.20 highlighted in bold

[b] *P* values ≤ 0.15 highlighted in bold

[c] *P* values ≤ 0.05 highlighted in bold. None of the interaction terms were significant; therefore, they were not included in the model

Finally, use of NSAIDs was also associated with higher non-adherence which could signify that patients are more likely to discontinue their ARM if it is an NSAID. In regard to discontinuation of csDMARDs and/or bDMARDs, use of bDMARDs was significantly associated with a lower hazard for non-adherence which could signify that patients are less likely to discontinue their ARM if it is a bDMARD. Interestingly, in this analysis, unlike the overall ARM analysis where increased DAS28-ESR was associated with higher hazard for discontinuation, higher HAQ-DI was associated with a lower hazard for discontinuation suggesting inherent differences in the determinants of non-adherence based on the type of ARMs.

We also examined other previously investigated factors that might have predicted non-adherence, including age, gender, education level, and annual house income, as well as novel factors that we hypothesized might have an impact on patient adherence to ARMs, such as physician age and gender and distance between residential area and clinics, but none of these factors was significantly associated with non-adherence. Other studies were also unable to show a significant association between ARM non-adherence and some of these factors such as age, gender, and education but, as mentioned above, contradictory results can be found in the literature regarding these parameters [8, 10–12].

Table 3 Time to csDMARDs/bDMARDs discontinuation due to patient's decision

	HR (95% CI), *p* value		
	Univariate analysis[a] N_{Events} = 167	Multivariate saturated analysis[b] N_{Events} = 91	Backward stepwise regression analysis[c] N_{Events} = 91
Sociodemographics			
Age (years)	**0.99 (0.98–1.00), 0.09**	0.99 (0.98–1.01), 0.35	–
Female gender	1.18 (0.80–1.75), 0.41	–	–
Marital status			
Single/widowed/divorced	Ref	–	–
Married	0.83 (0.60–1.14), 0.24		
Education status			
High school or less	Ref	–	–
Post-secondary	1.04 (0.76–1.42), 0.82		
Annual Income class during follow-up			
< $50,000	Ref	Ref	–
≥ $50,000	**1.42 (0.96–2.11), 0.08**	1.28 (0.80–2.04), 0.31	
Smoking history during follow-up			
Never smoked	Ref		–
Former smoker	0.97 (0.70–1.35), 0.86	–	
Current smoker	1.01 (0.64–1.61), 0.96		
Health insurance information			
Health insurance			
No private	Ref	–	–
Private	0.85 (0.58–1.25), 0.40		
% prescription covered by health insurance during follow-up	**1.02 (1.00–1.04), 0.05**	**1.02 (0.99–1.03), 0.10**	1.02 (0.99–1.04), 0.13
Disease characteristics			
Disease duration at baseline (years)	1.01 (0.99–1.03), 0.37	–	–
Early RA			
No	Ref	Ref	–
Yes	**1.25 (0.90–1.74), 0.19**	1.06 (0.64–1.74), 0.83	
Ever presence of erosion			
No	Ref	–	–
Yes	0.96 (0.82–1.12), 0.57		
RF positive			
No	Ref	–	–
Yes	0.89 (0.62–1.27), 0.52		
DAS28-ESR during follow-up	0.94 (0.84–1.06), 0.33	–	–
Physician global during follow-up	1.00 (0.94–1.07), 0.95	–	–
HAQ-DI during follow-up	**0.71 (0.57–0.87), 0.001**	**0.74 (0.50–1.09), 0.12**	**0.70 (0.50–0.97), 0.03**
Number of comorbidities during follow-up	**0.88 (0.80–0.96), 0.01**	**0.90 (0.78–1.04), 0.14**	0.89 (0.78–1.03), 0.11
Medication information			
Prior csDMARDs use at baseline			
No	Ref	–	–
Yes	1.08 (0.70–1.67), 0.73		
Prior bDMARDs use at baseline			
No	Ref	Ref	–
Yes	**0.66 (0.46–0.94), 0.02**	0.62 (0.27–1.42), 0.26	
	1.03 (0.93–1.14), 0.63	–	–

Table 3 (continued)

	HR (95% CI), *p* value		
	Univariate analysis[a] N_{Events} = 167	Multivariate saturated analysis[b] N_{Events} = 91	Backward stepwise regression analysis[c] N_{Events} = 91
Number of prior csDMARDs at baseline			
Number of prior bDMARDs at baseline	**0.84 (0.69–1.01), 0.07**	**1.44 (0.99–2.10), 0.06**	1.21 (0.94–1.56), 0.15
csDMARDs use during follow-up			
No	Ref	–	–
Yes	1.24 (0.85–1.80), 0.27		
bDMARDs use during follow-up			
No	Ref	Ref	Ref
Yes	**0.54 (0.39–0.76), 0.0004**	**0.48 (0.29–0.80), 0.01**	**0.50 (0.30–0.81), 0.01**
Steroid use during follow-up			
No	Ref	–	–
Yes	0.87 (0.59–1.29), 0.49		
NSAIDs use during follow-up			
No	Ref	Ref	–
Yes	**1.39 (0.96–2.01), 0.08**	1.28 (0.77–2.12), 0.34	
Total number of ARMs during follow-up	0.96 (0.83–1.11), 0.61	–	–
Physician information			
Female physician gender	0.89 (0.64–1.22), 0.46	–	–
Physician academic position			
Community-based	Ref	–	–
Academic or mixed based	0.98 (0.72–1.33), 0.87		
Residential address			
Urban	Ref	–	–
Rural	1.16 (0.78–1.72), 0.48		
Distance between residential and clinical site			
≤ 25 km	Ref	Ref	–
> 25 km	**1.24 (0.91–1.70), 0.18**	1.35 (0.87–2.09), 0.18	

[a] *P* values ≤ 0.20 highlighted in bold

[b] *P* values ≤ 0.15 highlighted in bold

[c] *P* values ≤ 0.05 highlighted in bold. None of the interaction terms were significant; therefore, they were not included in the model

A strength of the current study relates to the fact that we have tried to distinguish between non-intentional (e.g., due to forgetfulness) and intentional (based on the patient's decision to not take medication) non-adherence, considering only the latter, a non-adherence definition concern which has been previously raised in the literature [7]. Furthermore, the use of a comprehensive set of factors potentially affecting adherence which ranged from sociodemographics to health insurance coverage and physician practice characteristics, increases the internal validity of our findings. In terms of limitations, we could not investigate the effect of race and language appropriately as 85% of patients were Caucasian and 92% spoke English. It is also possible that some predictors of non-adherence were not identified as statistically significant due to lack of statistical power, particularly in the subset analysis exploring determinants of non-adherence to csDMARDs and/or bDMARDs.

In conclusion, we have assessed and identified factors associated with patient non-adherence to ARMs in routine clinical practice in Ontario; a variety of factors encompassing sociodemographic, disease, and medication characteristics was identified as significant independent predictors of non-adherence. These results should be taken into consideration when developing patient adherence support programs and in the choice of treatment regimens.

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