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RESEARCH ARTICLE

Changes in Market Share of Biologic and Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs for Treatment of Rheumatoid Arthritis: Results from the Ontario Best-Practice Research Initiative Database

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Abstract: ***Objective*:** For patients with Rheumatoid Arthritis (RA) who do not achieve adequate clinical response with combined conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), initiation of advanced therapies such as biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is recommended. Tumour necrosis factor inhibitors (TNFi) are the oldest and most commonly used subgroup of advanced therapies. In the last decade, new non-TNFi advanced therapy options have become available. We described the relative use of TNFi *vs*. non-TNFi in Ontario-based practices from 2008-2017.

***Methods*:** Adult patients with RA enrolled in the Ontario Best Practices Research Initiative (OBRI) database who started bDMARDs or tsDMARDs anytime during or within 30 days prior to enrollment were included. The proportion of patients treated with TNFi *vs*. non-TNFi agents between 2008 and 2017 was described for all patients and those initiating their first bDMARD/tsDMARD. All TNFi therapies were included. Non-TNFi included Abatacept, Rituximab, Tocilizumab, and Tofacitinib.

***Results*:** A total of 1,057 patients were included, of whom 72.0% were bDMARD/tsDMARD naïve. In 2008, the relative non-TNFi use was 5.4% in all patients while it was 0% in bDMARD/tsDMARD-naïve patients. In 2017, the proportion of patients using non-TNFi increased to 33.8% among all patients and 33.3% in bDMARD/tsDMARD-naïve patients.

***Conclusion*:** This descriptive analysis of data from the OBRI cohort reveals that TNFi are still used in the majority of cases; however, there has been an increase in the use of non-TNFi therapies both overall and as first-line advanced therapy. This trend towards non-TNFi therapies as first-line advanced therapy may be partially explained by the shift in guideline recommendations from TNFi as first-line to any of the advanced therapeutics.

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1. INTRODUCTION

1.1. Significance and Innovations

Each year from 2008-2017, TNFi agents have been used more frequently than non-TNFi therapies for the management of Rheumatoid Arthritis that has not been controlled with conventional synthetic DMARDs.

Relative non-TNFi advanced therapy use increased overtime in all patients (5.4% to 33.8%) and in those naive to advanced therapy (0% to 33.3%) from 2008 to 2017.

The largest increase in relative non-TNFi advanced therapy use in biologic-naive patients was seen between 2014 (14.4%) and 2016 (35.6%). It should be noted that there was a major shift in the ACR recommendations in the 2015 RA

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treatment guidelines to allow Rheumatologists to choose more freely between all TNFi and non-TNFi agents in selecting a first-line advanced therapy option.

1.2. Background

Rheumatoid arthritis (RA) is the most prevalent autoimmune inflammatory disease worldwide [1]. It is a chronic disease which affects persons of all ages and, if untreated, progresses to joint damage, deformation, and disability [1]. Patients with Rheumatoid Arthritis are typically treated with combined conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), such as methotrexate and leflunomide, or methotrexate in combination with sulfasalazine and hydroxychloroquine (triple therapy) [1]. If combination csDMARD-therapy fails to achieve low disease activity, the next step in goal-directed therapy is the initiation of either biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs); bDMARDs include tumour-necrosis factor inhibitors (TNFi) or non-TNFi classes [1, 2]. TNFi therapies were first approved for the treatment of RA by the Food and Drug Administration (FDA) in 1998, prior to any of the non-TNFi therapies lending to over two decades of Rheumatologist experience with their use [3]. The two Rheumatology associations that produce the most well-known guidelines for the management of Rheumatoid Arthritis, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), both suggest that TNFi bDMARDs, non-TNFi bDMARDs, and tsDMARDs can be initiated in any order, after inadequate csDMARD response, in order to achieve low disease activity, that is "treat-to-target" [1, 2, 4]. This is in contrast to the 2008 ACR guidelines which suggest treatment with TNFi first.

The Ontario Best Practice Research Initiative (OBRI) is a database of approximately 3,500 RA patients under the care of Rheumatologists in both academic and community settings from across Ontario. A significant portion of those enrolled are being treated with either bDMARDs or tsDMARDs. In the last decade, many new advanced RA treatment options, particularly in the non-TNFi classes including Tocilizumab, Abatacept, Rituximab, and Tofacitinib, have been approved and have ultimately become available for clinical use in Canada [5, 6]. As of 2017, Baricitinib had recently been approved in Canada but public reimbursement was still pending [7]. The guidelines do not recommend one type of advanced therapy over another because the available trials do not clearly identify the superiority of one agent, or agent class, over another [8-13].

Few publications have analyzed the change in market share of TNFi *vs*. non-TNFi advanced therapies over time in the context of overall usage and usage in bDMARD-naïve patients. Three retrospective Italian, Japanese, and US database analyses have assessed changes in relative biologic market share by individual drug with a focus on cost burden, all reporting an overall increase in biologic use with time as represented by increased health-care expenditure [14-16]. The studies by Sugiyama and Atzinger demonstrated an overall increase in the non-TNFi market share with time, as represented by cost, but the specific market share of the different classes is not stated [15, 16]. Herein we describe the temporal evolution of TNFi versus non-TNFi market share in Ontario-based practices from January 2008 to December 2017 in both all-comers and patients naïve to advanced therapeutics.

2. METHODS

2.1. Study Setting

OBRI is a Canadian multicenter registry which collects routine care data from rheumatologists across Ontario. Data is also collected from patients through telephone interviews. All patients have a rheumatologist-confirmed diagnosis of RA that was made after the age of 16, are at least 18 years of age and have at least one swollen joint at the time of registry enrollment. Institutional ethics has been granted (REB# is 07-0729 AE) and each patient, at the time of study enrollment, provided informed consent. The investigations conducted for this publication were done in compliance with the principles of the Declaration of Helsinki [17].

2.2. Study Population and Data Collection

Patients enrolled in OBRI between January 2008 and December 2017 who initiated treatment with advanced therapy (bDMARD or tsDMARD) within 30 days prior to, or anytime following enrollment in OBRI, were included in the analysis. Use of TNFi *vs*. non-TNFi during each calendar year was assessed among all users as well as those initiating their first advanced therapy (Fig. **1**).

The patient profile at the time of initiating advanced therapy was described, including sociodemographic parameters, smoking history, date of first advanced therapy, health insurance information, disease characteristics, number of co-morbidities, previous and ongoing RA treatments. Due to the relatively small number of those started on non-TNFi agents, all non-TNFi data were aggregated for the purpose of this analysis. TNFi included Etanercept, Adalimumab, Certolizumab, Golimumab, and Infliximab, including biosimilars of Etanercept and Infliximab. Non-TNFi included Abatacept, Rituximab, Tocilizumab, and Tofacitinib.

2.3. Statistical Analysis

Descriptive statistics, specifically mean and standard deviation (SD) for continuous variables and counts and proportions for categorical variables, were produced for all baseline characteristics. Comparisons between patients on TNFi *vs*. non-TNFi were conducted using the independent-samples t-test for continuous variables and the chi-square or the Fisher's Exact test, as appropriate, for categorical variables.

The primary analysis assessed yearly changes in market share of biologics dichotomized into TNFi and non-TNFi agents in all patients and those who were biologic naïve at the time of drug initiation; the analysis was descriptive in nature.

There were three secondary analyses. First, a sensitivity analysis assessing frequency of first advanced therapy use (excluding Rituximab) according to mechanism of action by calendar year. Second, an analysis of second-line therapy

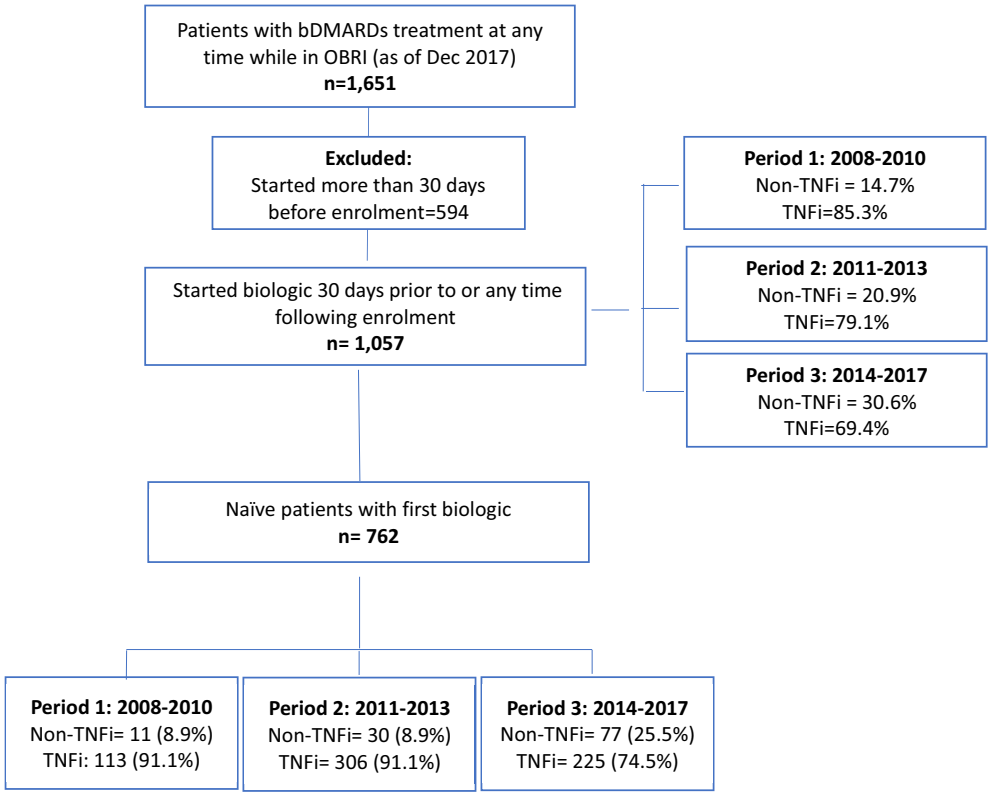

Fig. (1). Study flowchart.

after initial TNFi failure. Third, an exploratory multivariate logistic regression was conducted utilizing the collected baseline characteristics for the bDMARD/tsDMARD naïve cohort to identify factors predictive of selecting non-TNFi, as opposed to TNFi, as first-line advanced therapy. 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. The factors considered were patient's age, gender, disease-related factors, other RA concurrent medication and socio-economic characteristics. Diseases related factors included disease duration, disease activity score (DAS-28 ESR), physician global score, health assessment questionnaire disability index (HAQ-DI), HAQ pain, and number of comorbidities. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

3. RESULTS

3.1. Patient Socio-Demographic and Clinical Characteristics

3.1.1. Overall Study Population

A total of 1,057 patients were included in the primary analysis, of whom 74.0% used TNFi and 26.0% used non-TNFi during the study time. The average age (SD) was 56.6 (12.8), 79.8% were female, 80% were Caucasian, and 15% were current smokers (Table **1**).

3.1.2. Advanced Therapy Naïve Cohort

A total of 762 patients starting on their first biologic or targeted synthetic DMARD were included in the analysis. Of these, 644 (84.5%) were treated with TNFi while 118 (15.5%) were treated with non-TNFi agents (Table **2**). The mean (SD) age was 56.6 years (12.8), 79.5% of the cohort were females, 82.0% were Caucasian, and 16.3% were current smokers.

3.1.3. TNFi vs. Non-TNFi Therapy - Advanced Therapy Naïve Cohort

Key differences between the TNFi and non-TNFi treatment groups among patients without prior advanced therapy can be seen in Table **2**. A significantly higher proportion of patients in the non-TNFi group had a post-secondary level of education (66.1% *vs*. 56.2%; p=0.03) and had access to private health insurance (81.4% *vs*. 74.1%; p=0.02) compared to the TNFi group. Patients treated with non-TNFi were older (mean [SD]: 59.1 [12.8] *vs*. 56.1 [12.8] years; p=0.02) and more likely to have higher number of comorbidities (mean [SD]: 4.7 [3.2] *vs*. 3.9 [2.6] years; p=0.005). There was a marked difference in the frequency of non-TNFi use *vs*. TNFi use over the time period: 47.5% of TNFi use occurred in 2011-2013 compared with 25.4% of non-TNFi use. In contrast, 34.9% of TNFi and 65.3% of non-TNFi use occurred in 2014-2017(Table **2**). No differences in disease activity and severity were observed at the time of drug initiation (Table **2**).

Table 1. Patient profile of all patients at study initiation; overall and by the mechanism of action.

-	Total (n=1057)	TNFi (n=844)	NON-TNFi (n=213)	*p*-value
Demographic Factors				
Age, mean (SD)	56.6 (12.8)	56.3 (12.8)	57.9 (12.5)	0.11
Female gender, n (%)	844 (79.8%)	671 (79.5%)	173 (81.2%)	0.58
Marital status, married, n (%)	695 (65.8%)	558 (66.1%)	137 (64.3%)	0.59
Caucasian race, n (%)	846 (80.0%)	678 (80.3%)	168 (78.9%)	0.65
Education status, post-secondary, n (%)	600 (56.8%)	469 (55.6%)	131 (61.5%)	0.12
Annual income class (≥ 50,000 CD), n (%)[√]	409 (38.7%)	324 (38.4%)	85 (39.9%)	0.88
Smoking history, n (%)				
Never smoked	476 (45.0%)	384 (45.5%)	92 (43.2%)	0.06
Former smoker	354 (33.5%)	270 (32.0%)	84 (39.4%)	
Current smoker	159 (15.0%)	135 (16.0%)	24 (11.3%)	
Health insurance Plan, n (%)[Ω]				
Ontario Health Insurance Plan (OHIP) plus private	771 (72.9%)	602 (71.3%)	169 (79.3%)	**0.02**
Disease Factors				
Disease duration since diagnosis, mean (SD)	9.5 (9.7)	8.9 (9.3)	11.9 (10.8)	**<0.0001**
Early RA (≤ 1 year since diagnosis), n (%)	146 (13.8%)	124 (14.7%)	22 (10.3%)	0.10
RF positive, n (%)[π]	730 (69.1%)	594 (70.4%)	136 (63.8%)	0.62
Swollen joint count (0-28), mean (SD)[±]	7.0 (5.0)	6.7 (4.8)	8.0 (5.7)	**0.01**
Tender joint count (0-28), mean (SD)[β]	7.2 (6.4)	7.1 (6.3)	7.6 (6.8)	0.36
Physician Global (0-10), mean (SD)[¥]	5.1 (2.3)	5.1 (2.2)	5.2 (2.5)	0.79
Patient Global (0-10), mean (SD)[©]	5.5 (2.7)	5.4 (2.7)	5.6 (2.7)	0.54
DAS28-ESR, mean (SD) [×]	4.7 (1.4)	4.7 (1.4)	4.8 (1.5)	0.37
CDAI, mean (SD) [≠]	25.0 (12.8)	24.6 (12.5)	26.7 (14.2)	0.07
HAQ-DI, mean (SD) [∞]	1.3 (0.8)	1.3 (0.7)	1.5 (0.8)	0.32
HAQ-pain, mean (SD) [∞]	1.7 (0.8)	1.7 (0.8)	1.8 (0.9)	0.31
Presence of erosion, n(%)	497 (47.0%)	403 (47.7%)	94 (44.1%)	0.62
Number of comorbidities, mean (SD)	4.2 (2.8)	4.0 (2.7)	5.0 (3.1)	**0.0004**
Medication Factors				
Prior use of csDMARDs, n (%)	949 (89.8%)	747 (88.5%)	202 (94.8%)	**0.02**
Concurrent csDMARDs use, n (%)	742 (70.2%)	609 (72.2%)	133 (62.4%)	**0.01**
Concurrent steroid use, n (%)	224 (21.2%)	166 (19.7%)	58 (27.2%)	**0.01**
Concurrent NSAIDs use, n (%)	202 (19.1%)	170 (20.1%)	32 (15.0%)	0.10
Physician academic affiliation, n (%)	367 (34.7%)	284 (33.7%)	83 (39.0%)	0.14

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SD=standard deviation

DAS28 ESR=Disease Activity Score 28-erythrocyte sedimentation rate, csDMARDs=conventional synthetic disease-modifying antirheumatic drug, HAQ-DI=Health Assessment Questionnaire - Disability Index, RA=rheumatoid arthritis, RF=rheumatoid factor, TNFi=tumour necrosis factor inhibitor

Table 2. Patient profile of biologic-naïve at initiation of first advanced therapy: overall and with respect to mechanism of action.

-	Total (n=762)	By Mechanism of Action		
		TNFi (n=644)	NON-TNFi (n=118)	*p*-value
Demographic Factors				
Age, mean (SD)	56.6 (12.8)	56.1 (12.8)	59.1 (12.8)	**0.02**
Female gender, n (%)	606 (79.5%)	513 (79.7%)	93 (78.8%)	0.83
Marital status, married, n (%)	519 (68.1%)	440 (68.3%)	79 (66.9%)	0.93
Caucasian race, n (%)	625 (82.0%)	532 (82.6%)	93 (78.8%)	0.83
Education status, post-secondary, n (%)	440 (57.7%)	362 (56.2%)	78 (66.1%)	**0.03**

(Table 2) contd….

-	Total (n=762)	By Mechanism of Action		
		TNFi (n=644)	NON-TNFi (n=118)	*p*-value
Annual income class (≥ 50,000 CD), n (%)[√]	305 (40.0%)	256 (39.8%)	49 (41.5%)	0.94
Smoking history, n (%)				
Never smoked	345 (45.3%)	297 (46.1%)	48 (40.7%)	0.19
Former smoker	256 (33.6%)	209 (32.5%)	47 (39.8%)	
Current smoker	124 (16.3%)	109 (16.9%)	15 (12.7%)	
Health insurance Plan, n (%)[Ω]				
Ontario Health Insurance Plan (OHIP) plus private	573 (75.2%)	477 (74.1%)	96 (81.4%)	**0.02**
Disease Factors				
Disease duration since diagnosis, mean (SD)	7.9 (8.7)	7.7 (8.5)	8.7 (9.7)	0.26
Early RA (≤ 1 year since diagnosis), n (%)	125 (16.4%)	107 (16.6%)	18 (15.3%)	0.71
RF positive, n (%)[π]	523 (68.6%)	450 (69.9%)	73 (61.9%)	0.81
Swollen joint count (0-28), mean (SD)[±]	6.6 (4.7)	6.5 (4.5)	7.5 (5.3)	0.09
Tender joint count (0-28), mean (SD)[β]	7.0 (6.4)	7.1 (6.4)	6.4 (6.0)	0.32
Physician Global (0-10), mean (SD)[¥]	5.0 (2.3)	5.1 (2.2)	4.9 (2.5)	0.50
Patient Global (0-10), mean (SD)[©]	5.3 (2.7)	5.3 (2.7)	5.5 (2.8)	0.58
DAS28-ESR, mean (SD) [×]	4.6 (1.4)	4.6 (1.4)	4.6 (1.5)	0.80
CDAI, mean (SD) [≠]	24.3 (12.3)	24.2 (12.3)	24.8 (12.1)	0.69
HAQ-DI, mean (SD) [∞]	1.3 (0.8)	1.2 (0.7)	1.4 (0.8)	0.11
HAQ-pain, mean (SD) [∞]	1.7 (0.9)	1.7 (0.8)	1.8 (0.9)	0.25
Presence of erosion, n(%)	336 (44.1%)	290 (45.0%)	46 (39.0%)	0.23
Number of comorbidities, mean (SD)	4.0 (2.8)	3.9 (2.6)	4.7 (3.2)	**0.005**
Medication Factors				
Prior use of csDMARDs, n (%)	664 (87.1%)	557 (86.5%)	107 (90.7%)	0.43
Concurrent csDMARDs use, n (%)	659 (86.5%)	560 (87.0%)	99 (83.9%)	0.55
Concurrent steroid use, n (%)	157 (20.6%)	130 (20.2%)	27 (22.9%)	0.46
Concurrent NSAIDs use, n (%)	155 (20.3%)	136 (21.1%)	19 (16.1%)	0.24
Time period of first bDMARD initiation, n (%) 2008-2010 2011-2013 2014-2017	124 (16.3%) 336 (44.1%) 302 (39.6%)	113 (17.6%) 306 (47.5%) 225 (34.9%)	11 (9.3%) 30 (25.4%) 77 (65.3%)	**<0.0001**
Physician academic affiliation, n (%)	245 (32.2%)	201 (31.2%)	44 (37.3%)	0.18

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SD=standard deviation

DAS28 ESR=Disease Activity Score 28-erythrocyte sedimentation rate, csDMARDs=conventional synthetic disease-modifying antirheumatic drug, HAQ-DI=Health Assessment Questionnaire - Disability Index, RA=rheumatoid arthritis, RF=rheumatoid factor, TNFi=tumour necrosis factor inhibitor.

3.2. Primary Analysis of Relative Use of TNFi and Non-TNFi Therapy Over Time

For both the total population as well as the bDMARD/tsDMARD naïve cohort, there was a clear increase in the relative use of non-TNFi therapy as each calendar year progressed. In 2008, 5.4% of the cohort were using non-TNFi therapy. This proportion increased to 24% in 2013 and 33.8% in 2017. There was an overall decline in the number of patients using advanced therapies in 2017, when compared to previous years (Fig. **2**).

A similar trajectory was noted in the biologic naïve cohort with an overall increase in the proportional use of first-line non-TNFi therapy over time. In 2008, 0% of the biologic naïve cohort was using first-line non-TNFi therapy. This proportion increased to 12.5% in 2013 and 35.6% in 2016. Just as in the overall cohort, there was a decrease in advanced therapy use in 2017 to a total of 40 patients, down from 87 patients the year prior (Fig. **3**). A sensitivity analysis excluding patients started on Rituximab revealed similar results (Appendix **1**).

3.3. Secondary Analyses

3.3.1. Second Line Therapy after Initial TNFi Discontinuation

127 patients in the bDMARD/tsDMARD naïve cohort started a second advanced therapeutic option after discontinuing their first TNFi, of whom 68/127 (53.5%) initiated non-TNFi therapy. (Appendix **2**). As stated above, an increasing trend was observed in the use of non-TNFi agents following the discontinuation of the first TNFi (Fig. **4**).

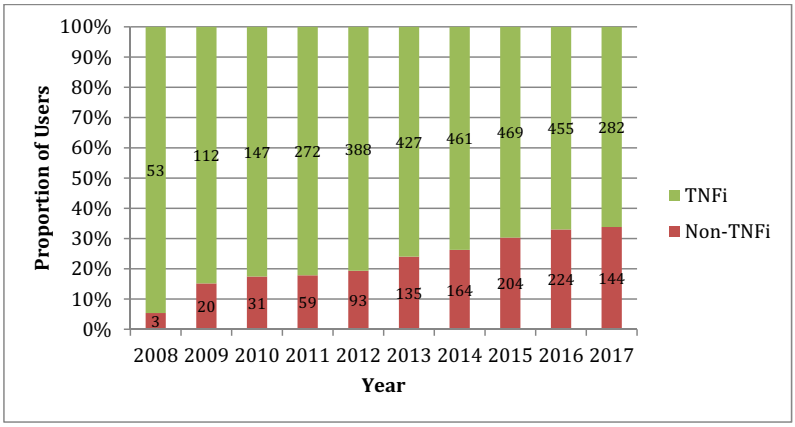


Fig. (2). Frequency of advanced therapy use according to the mechanism of action by calendar year (n=1057). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

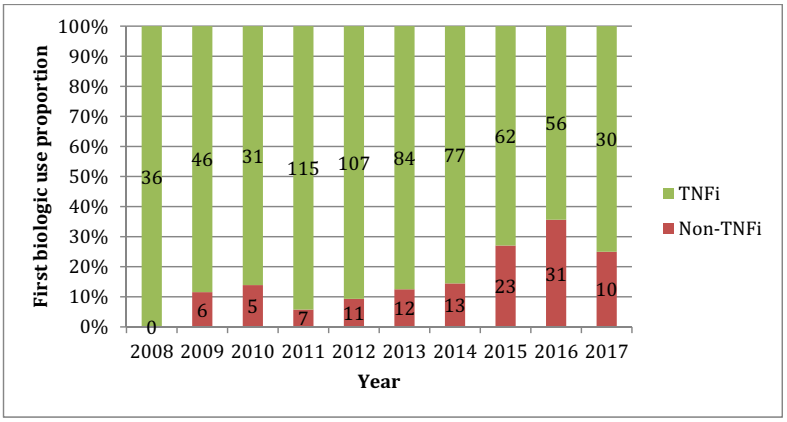


Fig. (3). Frequency of first advanced therapy use according to the mechanism of action by calendar year (n=762). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

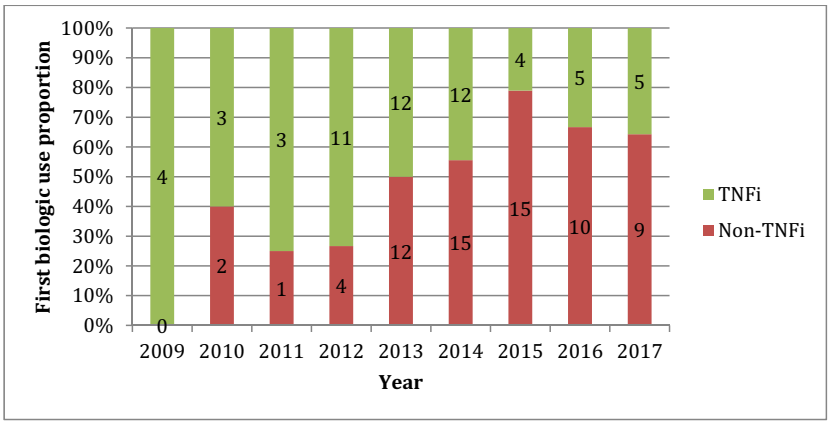


Fig. (4). Frequency of second advanced therapy use after TNFi discontinuation according to the mechanism of action by calendar year (n=127). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.3.2. Regression Analysis to Assess Predictors of Non-TNFi Use at Initiation of bDMARD/tsDMARD

Univariate analysis revealed non-TNFi agent use to be associated with the increased number of comorbidities (OR 1.10, p=0.01) and recent drug initiation (OR 3.52, p<0.0001), when comparing the period of 2014-2017 to 2008-2010. This was confirmed in multivariate analysis (OR 4.33; Appendix **3**).

4. DISCUSSION

Longitudinal analysis of real-world Canadian market share of bDMARDs and tsDMARDs revealed increased use of non-TNFi advanced therapeutics over time, in both the total population and biologic-naïve patients. Still, TNFi use remains by far the most prevalent. In the total study population, the relative proportion using non-TNFi agents increased incrementally from 5.4% in 2008 to 33.8% in 2017. Similar changes were described in Japan [15]. In the biologic naïve population, we report increasing non-TNFi market shares from 0% in 2008 to 33.3% in 2017.

Other observational studies evaluating the frequency of non-TNFi have reported similar trends of increased use over time. The United States National Data Bank for Rheumatic Diseases (NDB) reports limited non-TNFi (2.5%) use between 1998-2011 [18], while the Swedish Quality Register (SQR) reports relative use of non-TNFi as the first biologic to be 18.1% between 2011-2015 [19]. These studies are in agreement with our finding that non-TNFi usage is higher in recent years.

Although we cannot ascertain the exact reasons for increased relative non-TNFi use over-time in our cohort, we propose a number of possibilities. The first is that as time elapsed, the number of non-TNFi therapies available for use increased. A rheumatologist practicing in 2017 has far more non-TNFi therapies to choose from when compared to 2008. The sheer number of options allowed the treating rheumatologists to diversify their treatment protocols, driving the relative number of patients using non-TNFi up. The second proposal is that the intervening decade between 2008 and 2017 allowed for rheumatologists to gain experience, and therefore comfort, in prescribing non-TNFi therapies, which likely translates to an increase in prescription. Prior to the latest ACR and EULAR guidelines, prescribers would wait for their patients to fail a TNFi before advancing to non-TNFi therapy [1, 2, 20, 21]. Within this framework, every patient using non-TNFi therapy was once a patient who used TNFi. The third proposal is that updated guideline support of the option to use non-TNFi therapy immediately after the failure of combined csDMARDs translates into the development of a new cohort of biologic-naïve patients now receiving non-TNFi therapy [1, 2, 20, 21]. TNFi therapy is still more commonly prescribed than non-TNFi in biologic-naïve patients. That being said, patients who have failed TNFi therapy often move on to non-TNFi as their second or third advanced therapies. The fourth proposition relates to the fact that these patients within our cohort who have failed TNFi therapy are likely to switch to non-TNFi therapy. From 2008 to 2017, an increasing number of patients in the analyzed cohort would have made this transition, driving the proportion of non-TNFi up by replacement. Lastly, with the publication of the ADACTA trial in 2013, which demonstrated better DAS28 response in Tocilizumab (non-TNFi) monotherapy compared to Adalimumab (TNFi) monotherapy, rheumatologists may have been encouraged to opt for the use of Tocilizumab, a non-TNFi option in the significant portion of patients who do not tolerate csDMARDs, further increasing the relative non-TNFi use in this poplation [8].

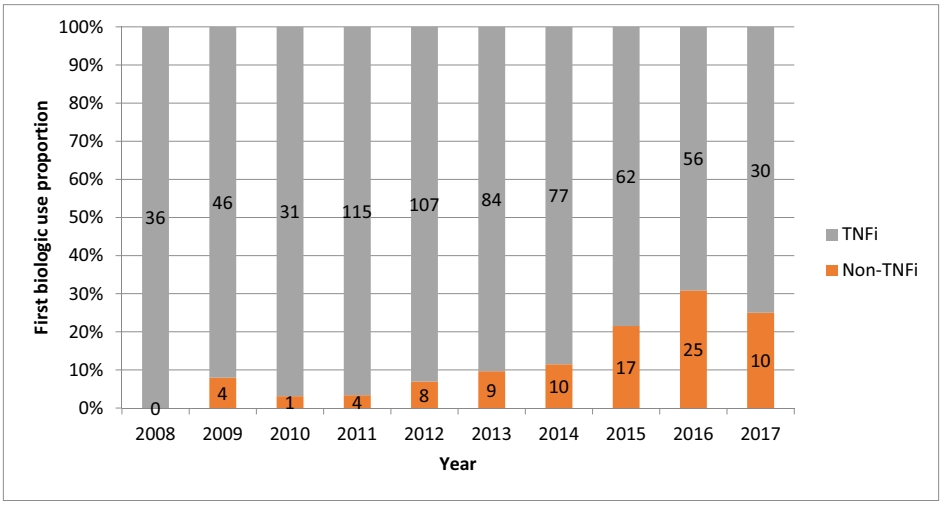
Evidence suggests that TNFi and non-TNFi have similar efficacy and drug survival. Our group has examined rates of discontinuation by class, and reason for indication within the OBRI database. Rates of discontinuation were similar between TNFi and non-TNFi (44.6% over a median follow-up of 1.7 years) [22]. Moreover, no differences were found by comparing TNFi to non-TNFi with respect to the reason for discontinuation [22]. Given this lack of clear reason to choose non-TNFi over TNFi in patients starting their first advanced therapy, we conducted an exploratory analysis to determine predictors of first-line non-TNFi use in our cohort. Our regression model demonstrated two predictors of non-TNFi therapy use in biologic naïve patients. The first confirmed that the later year of prescribing was strongly correlated (OR >4 in multivariate analysis) with the prescription of non-TNFi. Second, we found that the number of comorbidities similarly predicted non-TNFi use. Our best account for the second finding is that TNFi is contraindicated in heart failure and cardiomyopathy [23]. The strengths of our study include the fact that all data is collected prospectively, which avoids the risk of recall bias and ensures that all demographic and drug-related data are accurately collected. Additionally, the nine-year length of follow-up reveals how paradigmatic advances in therapy and guidelines translate to practice patterns.

The major limitation of our study is possible sampling bias in that only selected academic centres and community offices participate in data collection. These providers may not be representative of the national rheumatology community. This limitation is perhaps less serious given OBRI's excellent representation of both community and academic rheumatologists. Nationwide databases such as the Swedish Quality Register are able to capture all patients who have been prescribed the medications assessed in this study to avoid the aforementioned sampling bias.

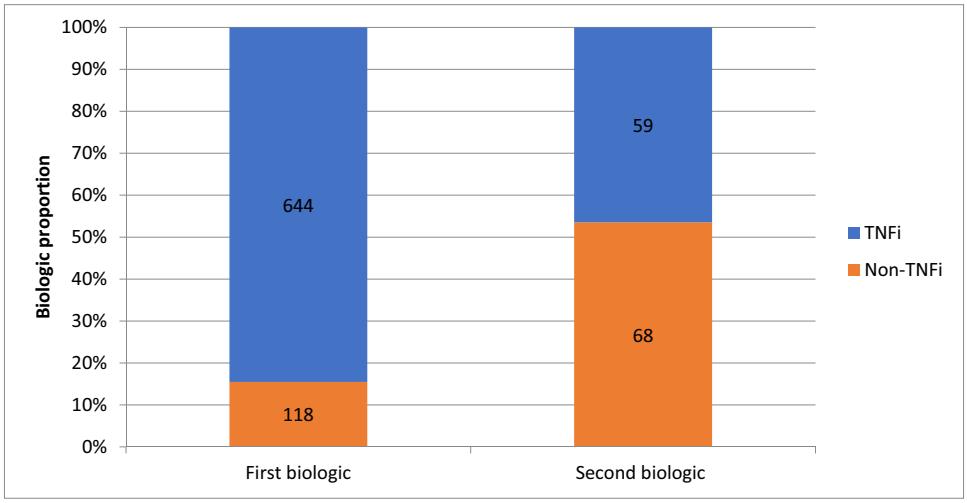
CONCLUSION

Our observational study reveals increased relative usage and market share of non-TNFi in both biologic-naïve and all-comers, yet TNFi usage remains predominant. This is in accordance with other studies as well as evolving practice guidelines. Ontario Rheumatologists appear to be appropriately adjusting their practice patterns to reflect the evolving treatment landscape of rheumatoid arthritis. At this time, we are unaware of specific patient-related factors that predict individual drug class response. Over time, we hope that the use of genomics, cytokine analysis, and flow-cytometric testing patient-specific therapy selection can be achieved. As more agents enter the market, there will be a role for prospective head-to-head comparison and directed cost-effectiveness analyses to help guide future use for patients, prescribers, and payers alike.

APPENDICES



Appendix 1. Frequency of first advanced therapy use excluding Rituximab according to mechanism of action by calendar year (n=732). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



Appendix 2. Mechanism of action of first advanced therapy and second post-TNFi discontinuation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Appendix 3. Predictors of use of Non-TNFi *vs.* TNFi at initiation of first advanced therapy.

-	Univariate Analysis[1]	Multivariate Saturated Analysis[2]	Backward Stepwise Regression Analysis[3]
	OR (95% CI), p-value	**OR (95% CI), p-value**	**OR (95% CI), p-value**
Demographic Factors			
-Age	**1.02 (1.00-1.04), 0.02**	1.01 (0.99-1.03), 0.31	-
-Gender			
Female *vs.* Male	0.95 (0.59-21.54), 0.83	1.11 (0.61-2.01), 0.73	-
-Marital status			

(Appendix 3) contd….

-	Univariate Analysis[1]	Multivariate Saturated Analysis[2]	Backward Stepwise Regression Analysis[3]
Married *vs*. Single/widowed/divorced	0.98 (0.64-1.50), 0.93	-	-
-Race			
Caucasian *vs*. Non-Caucasian	1.07 (0.58-1.97), 0.83	-	-
-Education status			
Post-secondary *vs*. High school or less	**1.59 (1.05-2.41), 0.03**	**1.47 (0.91-2.38), 0.12**	-
-Annual income class (CD)			
≥ 50,000 *vs*. < 50,000	1.02 (0.64-1.62), 0.94	-	-
-Smoking history			
Former smoking *vs*. Never smoking	**1.39 (0.90-2.16), 0.07**	1.29 (0.78-2.14), 0.21	**-**
Current smoking *vs*. Never smoking	**0.85 (0.46-1.58), 0.27**	0.87 (0.44-1.74), 0.43	-
-Health insurance Plan			
OHIP plus Private *vs*. OHIP	**2.07 (1.13-3.782), 0.02**	1.21 (0.57-2.58), 0.62	-
Disease Factors			
-Disease duration since diagnosis	1.01 (0.99-1.03), 0.26	-	-
-Disease onset			
Early RA *vs*. Established RA	0.90 (0.53-1.56), 0.71	-	-
-RF positive			
Yes *vs*. No	0.94 (0.59-1.52), 0.81	-	-
-Swollen joint count (0-28)	**1.05 (1.00-1.10), 0.05**	**1.04 (1.00-1.09), 0.08**	**-**
-Tender joint count (0-28)	0.98 (0.94-1.02), 0.32	-	-
-Physician Global (0-10)	0.96 (0.86-1.08), 0.49	-	-
-Patient Global (0-10)	1.03 (0.94-1.12), 0.57	-	-
-DAS28-ESR (0-9.4)	0.98 (0.82-1.16), 0.80	**-**	**-**
-CDAI (0-76)	1.00 (0.98-1.02), 0.69	-	-
-HAQ-DI (0-3)	1.30 (0.94-1.81), 0.29	**-**	**-**
-HAQ-pain (0-3)	1.19 (0.89-1.59), 0.25	-	-
-Presence of erosion	0.77 (0.50-1.18), 0.23	-	-
-Number of comorbidities	**1.10 (1.03-1.18), 0.01**	1.05 (0.97-1.14), 0.27	**-**
Medication Factors			
-Prior use of csDMARDs			
Yes *vs*. No	**0.68 (0.35-1.32), 0.26**		-
-Concurrent csDMARDs use			
Yes *vs*. No	0.84 (0.47-1.50), 0.55	-	-
-Concurrent steroid use			-
Yes *vs*. No	1.19 (0.75-1.92), 0.46	**-**	**-**
-Concurrent NSAIDs use			
Yes *vs*. No	0.73 (0.43-1.23), 0.24	-	-
Time period of first biologic used			
2008-2010 2011-2013 2014-2017	Ref **1.01 (0.49-2.08), 0.02** **3.52 (1.80-6.88), <0.0001**	Ref **1.12 (0.42-3.04), 0.08** **3.82 (1.43-10.2), <0.0001**	Ref 1.23 (0.48-3.15), 0.09 **4.33 (1.76-10.7), <0.0001**

[1] P-values ≤ 0.20 highlighted in bold
[2] P-values ≤ 0.15 highlighted in bold
[3] P-values ≤ 0.05 highlighted in bold

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been ethically approved by Institutional ethics committee of University Health Network, Canada (REB# is 07-0729 AE).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The reported experiments on human subjects were performed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent has been provided by each patient at the time of study.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

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All other authors declare no conflicts of interest. All authors meet the journal's criteria for authorship.

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