Time to Discontinuation of Biologic Therapy by Mechanism of Action in Rheumatoid Arthritis Patients: Results From The Ontario Best Practices Research Initiative (OBRI)

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BACKGROUND

- Patients with rheumatoid arthritis (RA) may discontinue their biologic disease modifying antirheumatic drug (bDMARDs) due to non-response, loss of response or adverse events. However, time to discontinuation may be related to mechanism of action of bDMARDs.
- Multiple publications previously compare drug survival between TNFi and Non-TNFi bDMARDs as well as reason for discontinuation, but there is paucity of data that compares drug retention rates stratified for reason for discontinuation in a realistic clinical setting.

OBJECTIVES

- We aimed to compare drug survival of tumor necrosis factor inhibitors (TNFi) versus Non-TNFi bDMARDs, when stratified for reason for discontinuation, in those initiating their first bDMARD treatment in the Ontario Best Practices Research Initiative (OBRI); an clinical registry for RA (OBRI-RA registry).

METHODS

- RA patients enrolled in the OBRI initiating their first bDMARD within 30 days prior to or anytime following enrolment were included in the analysis. Patients were excluded if they had less than 2 visits during this period of time.
- Time to discontinuation of bDMARD due to (1) any reason, (2) non-response, physician, and patient decision, (3) non-response, and (4) adverse events (AEs) were assessed using Kaplan-Meier survival analysis for TNFi versus Non-TNFi/Tofa users.
- Cox proportional hazards regression model was also used to compare TNFi versus Non-TNFi/Tofa users for time on biologic discontinuation adjusting for the effect of potential confounders. To deal with missing data, multiple imputation by chained equations was performed.

RESULTS

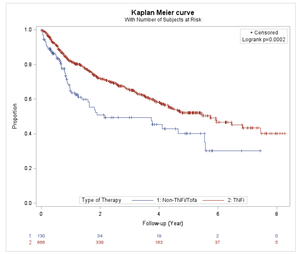
- A total of 796 patients were included of whom 130 (16.3%) received non-TNFi and 756 (83.7%) received TNFi (Table 1). **TNFi** included: Etanercept, Adalimumab, Certolizumab, Golimumab, and Infliximab and **Non-TNFi and Tofa** included: Abatacept, Rituximab, Tocilizumab, and small molecule Tofacitinib.
- Mean (SD) age and disease duration were 56.2 (12.8) years and 8.3 (9.0) years, respectively, and the majority were females (79.8%).
- Patients in the non-TNFi/Tofa group had significantly longer disease duration, higher swollen joint count, higher HAQ-DI, higher number of comorbidities, and were more likely to use csDMARDs prior to enrolment compared to patients in TNFi group (Table 1).
- Over a mean (SD) follow-up of 2.4 (2.0) years, bDMARD discontinuation was reported for 291 (36.6%) due to any reason, 229 (28.8%) due to non-response, AEs, physician, and patient decision, 110 (13.8%) due to non-response, and 81 (10.2%) due to AEs, respectively.
- There was a significant difference in time to discontinuation due to any reason (Logrank p=0.0002)(Figure 1a) ; non-response, AEs, physician, and patient decision (Logrank p=0.04)(Figure 1b) between TNFi and non-TNFi/Tofa users.
- However, there was no significant difference in bDMARD discontinuation due to non-response (Logrank p=0.36)(Figure 1c) and AEs (Logrank p=0.06)(figure 1d).
- After adjusting for potential confounders, difference in discontinuation was remained significant between the TNFi and non-TNFi/Tofa group for any reason [HR: 0.62 (0.46-0.84)] and non-response, AEs, physician, and patient decision [HR: 0.67 (0.47-0.94)](Table 2).

Table 1: Patient Profile at Initiation of First bDMARD; Overall and by Mechanism of Action

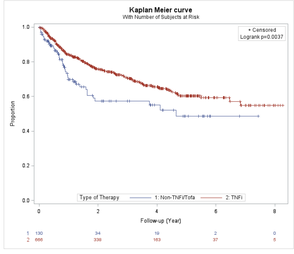
	TOTAL (N=796)	BY MECHANISM OF ACTION		
		Non-TNFi/Tofa (n=130)	TNFi (n=666)	p-value
Sociodemographic Factors				
- Age, mean (sd)	56.2 (12.8)	58.2 (12.7)	55.8 (12.8)	0.05
- Sex, Female, n (%)	635 (79.8)	103 (79.2)	532 (79.9)	0.87
- Annual income class (≥ 50,000 CD), n (%)	312 (39.2)	51 (39.2)	261 (39.2)	0.90
- Smoking history, n (%)				
Never smoking	363 (45.6)	61 (46.9)	302 (45.3)	0.24
Former smoking	262 (32.9)	46 (35.4)	216 (32.4)	
Current smoking	133 (16.7)	15 (11.5)	118 (17.7)	
Disease Factors				
- Disease duration, mean (sd)	8.3 (9.0)	10.3 (10.4)	8.0 (8.7)	**0.02**
- Disease early onset, n (%)	129 (16.2)	19 (14.6)	110 (16.5)	0.59
- RF positive, n (%)	546 (68.6)	86 (66.2)	460 (69.1)	0.65
- Swollen joint count (0-28) , mean (sd)	6.8 (4.9)	7.8 (5.3)	6.6 (4.8)	**0.02**
- Tender joint count (0-28) , mean (sd)	7.2 (6.4)	6.9 (6.2)	7.3 (6.4)	0.58
- Physician Global Assessment (0-10) , mean (sd)	5.1 (2.3)	5.0 (2.5)	5.1 (2.2)	0.68
- Patient Global Assessment (0-10) , mean (sd)	5.4 (2.7)	5.7 (2.8)	5.4 (2.7)	0.24
- DAS28-ESR (0-9.4) , mean (sd)	4.7 (1.4)	4.7 (1.5)	4.7 (1.4)	0.88
- CDAI (0-76) , mean (sd)	24.8 (12.6)	25.9 (12.9)	24.6 (12.6)	0.39
- HAQ-DI (0-3) , mean (sd)	1.3 (0.8)	1.5 (0.8)	1.3 (0.7)	**0.01**
- Number of comorbidities , mean (sd)	3.4 (2.9)	4.1 (3.3)	3.3 (2.8)	**0.01**
Medication Factors				
- Prior use of csDMARDs, n (%)	703 (88.3)	121 (93.1)	582 (87.4)	0.16
- Concurrent use of csDMARDs, n (%)	681 (85.6)	103 (79.2)	578 (86.8)	**0.03**
- Concurrent use of steroid , n (%)	168 (21.1)	29 (22.3)	139 (20.9)	0.71
- Concurrent use of NSAIDs use, n (%)	155 (19.5)	19 (14.6)	136 (20.4)	0.13

Figure 1: Kaplan-Meier Survival Curves for Time to Discontinuation of First bDMARD Based on Mechanism of Action

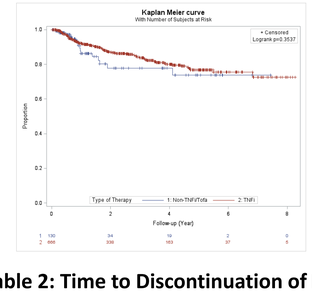
a. Due to Any Reason



b. Due to Non-Response, AEs, physician, and patient decision



c. Due to Non-Response



d. Due to AEs

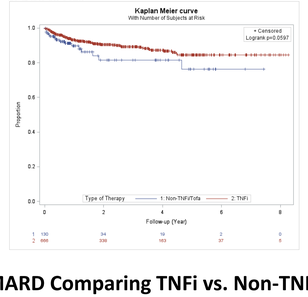


Table 2: Time to Discontinuation of First bDMARD Comparing TNFi vs. Non-TNFi/Tofa Using Cox Regression Models, Univariate and Multivariate Analysis

Reason for discontinuation	TNFi vs. Non-TNFi/Tofa Hazard Ratio (HR); 95% Confidence Interval (CI); p-value	
	Unadjusted models	Adjusted models after multiple imputation
Any reason	**0.58 (0.43-0.78), 0.0003**	**0.62 (0.46-0.84), 0.002***
Non-response, AEs, physician and patient decision	**0.61 (0.44-0.85), 0.004**	**0.67 (0.47-0.94), 0.02¥**
Non-response	0.78 (0.46-1.32), 0.35	0.89 (0.52-1.53), 0.67©
Adverse events	0.59 (0.34-1.03), 0.06	0.73 (0.41-1.28), 0.27*

* Adjusted model included patient age and gender as covariates; furthermore, variables that were significantly in univarite analysis (annual income class, former smoking, early onset of disease, swollen joint counts, HAQ-DI, comorbidity number and concomitant use of csDMARDs) were also considered.

¥ Adjusted model included patient age and gender as covariates; furthermore, variables that were significantly in univarite analysis analysis (annual income class, early onset of disease, swollen joint counts, and HAQ-DI, comorbidity number) were also considered.

© Adjusted model included patient age and gender as covariates; furthermore, variables that were significantly in univarite analysis analysis (annual income class, swollen joint counts, and HAQ-DI) were also considered.

Fonts in bold are statistically significant (p-value< 0.05).

CONCLUSIONS

- The analysis demonstrates that patients initially started on non-TNFi/Tofa therapy are significantly more likely to discontinue their therapy earlier for any reason and due to non-response, AEs, physician and patient decision compared to TNFi therapy.
- Lack of response is likely not driving this, however AEs and, to an even greater degree, patient and physician preference likely influenced the results.

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