Predictors of Treatment Changes in Patients With Rheumatoid Arthritis Using Machine Learning

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OBJECTIVE

To evaluate the application of machine learning to real-world data using electronic health records to predict factors associated with treatment changes among patients with rheumatoid arthritis

CONCLUSIONS

- Variables that increased the risk of switching to another mechanism of action: high non-rheumatic Charlson Comorbidity Index score, cancer chemotherapy, abnormal C-reactive protein
- Variables that increased the risk of cycling to another tumor necrosis factor inhibitor: psoriasis skin disorder, non-traumatic joint disorder
- Cyclers and switchers had similar use of procedures, hospitalizations, emergency room visits and outpatient visits

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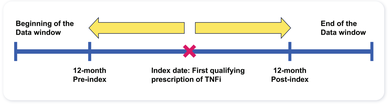
BACKGROUND

- Given treatment guidelines and options, understanding patterns of drug use in rheumatoid arthritis (RA) is critical

METHODS

- **Data Source:** Optum's MarketClarity® electronic health records (EHR) data (>80M patient records)
- **Study Cohort:** We identified a cohort of patients diagnosed with RA and initiating first line treatment with a tumor necrosis factor inhibitor (TNFi) (not previously treated with a biologic disease modifying antirheumatic drug [bDMARD] or targeted synthetic [ts]DMARD) from January 2011 to March 2019
- **Study Outcome:** 1) "cycling" from 1 TNFi to another and 2) "switching" from a TNFi to a non-TNFi bDMARD or tsDMARD within 12-months after TNFi initiation
- **Methods:** Machine learning modeling leveraging Bayesian methodology developing iPredict Models for predictors of treatment changes with an ensemble approach examined a network of at least 128 predictive models. 80% of patients were used to train our model; 20% were used to validate the model

Figure 1. Study Design



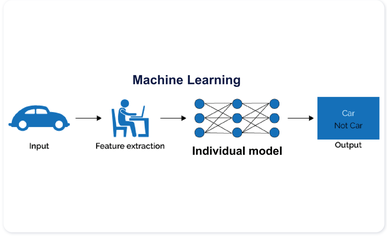
aMOA, another mode of action; TNFi, tumor necrosis factor inhibitor.
The index date is the date of first observation of a qualifying prescription of a TNFi. Eligible patients were followed for 1 year to see whether they switch to another TNFi (thus, experience TNF cycling), or switch from the index TNFi to aMOA.

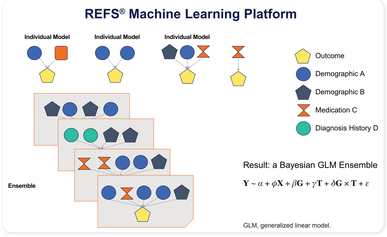
METHODS CONTINUED

Treatment Definitions

- **TNFi:** infliximab, adalimumab, certolizumab, etanercept, golimumab (TNFi bDMARD)
- **Another mode of action (aMOA)** (includes non-TNFi biologics and Janus kinase [JAK] inhibitors): tocilizumab, sarilumab, abatacept, rituximab, golimumab (non-TNFi bDMARD)
  - JAK inhibitors: tofacitinib, upadacitinib, baricitinib (tsDMARD)
- **Conventional synthetic (cs)DMARDs:** methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and cyclosporine
  - Patients were allowed to be treated with csDMARDs at any point during the study window, including the pre-index period

Figure 2. Machine Learning Methods (REFS)





REFS Uses an Ensemble of Models

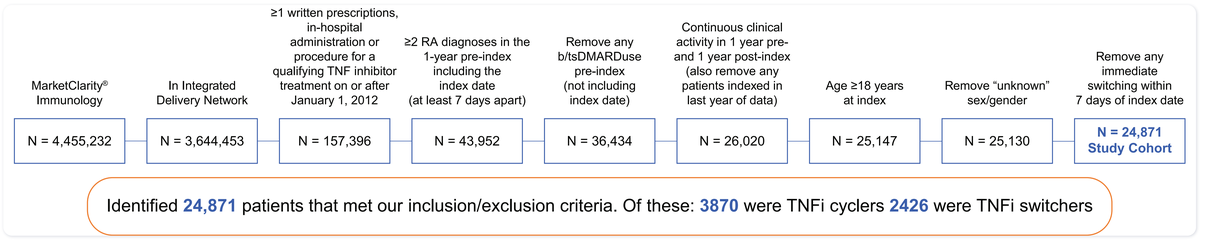
- In an underdetermined system, a single model has little predictive power
- An ensemble enables better sampling of the space of models and increases predictive power
- The ensemble amplifies relationships supported by the data and dilutes spurious ones

How REFS Builds Networks

- Metropolis-Hastings Markov Chain Monte Carlo algorithm to sample the posterior distribution of the model landscape
- Adds/removes edges; score and compare to previous network fragment; decides to accept/reject
- Adopts simulated annealing to speed up model learning and to avoid local optima

RESULTS

Figure 3. STROBE Diagram



Identified **24,871** patients that met our inclusion/exclusion criteria. Of these: **3870** were TNFi cyclers **2426** were TNFi switchers

Table 1. Demographics by Type of Treatment Switch

Demographic Characteristics	Overall		TNFi → TNFi		TNFi → aMOA		*P*-Value[a]
	N	%	N	%	N	%	
Number of Patients (N)	24,871	100	3870	100	2426	100	
Age							
Mean (SD)	54.98 (13.71)		52.00 (13.16)		54.49 (13.20)		<.01
Min | Median | Max	18 | 56 | 88		18 | 53 | 85		18 | 55 | 88		
							<.01
18–34	2106	8.5	420	10.9	191	7.9	
35–44	3203	12.9	626	16.2	326	13.4	
45–54	5936	23.9	1039	26.9	628	25.9	
55–64	7607	30.6	1150	29.7	747	30.8	
65–74	4188	16.8	496	12.8	390	16.1	
>75	1831	7.4	139	3.6	144	5.9	
Gender							.04
Female	19,194	77.2	3088	79.8	1987	81.9	
Male	5677	22.8	782	20.2	439	18.1	
Race							.23
African American	2324	9.3	279	7.2	191	7.9	
Caucasian	20,636	83.0	3274	84.6	2061	85.0	
Asian	297	1.2	52	1.3	21	0.9	
Other/Unknown	1614	6.5	265	6.9	153	6.3	

[a]For continuous variables, the *P*-value will be calculated using a Wilcoxon-Mann-Whitney test. For categorical variables, Fisher's exact test will be used.

Table 2. Healthcare Utilization by Type of Treatment Switch

Visit type	Overall		TNFi → TNFi		TNFi → aMOA		*P*-Value[a]
	N	%	N	%	N	%	
Number of Patients (N)	24,871	100	3870	100	2426	100	
All-cause							
Hospitalizations							.25
Mean (SD)	0.16 (0.56)		0.12 (0.51)		0.14 (0.57)		
Min | Median | Max	0 | 0 | 15		0 | 0 | 15		0 | 0 | 15		
0	22,062	88.7	3517	90.9	2191	90.3	.25
1	2117	8.5	274	7.1	170	7.0	
2+	692	2.8	79	2.0	65	2.7	
LOS in Days[b]	(N = 2809)		(N = 353)		(N = 235)		.19
Mean (SD)	6.08 (7.71)		5.18 (6.25)		5.93 (7.07)		
1st Quarter |Median |3rd Quarter	2 | 4 | 7		2 | 3 | 6		2 | 3 | 7		
Emergency Department Visits							.82
Mean (SD)	0.36 (1.10)		0.38 (1.13)		0.39 (1.02)		
Min | Median | Max	0 | 0 | 35		0 | 0 | 28		0 | 0 | 16		
0	20,013	80.5	3068	79.3	1908	78.7	.82
1	3016	12.1	492	12.7	316	13.0	
2+	1842	7.4	310	8.0	202	8.3	
Outpatient Visits							.44
Mean (SD)	19.40 (18.26)		22.47 (20.17)		22.06 (20.37)		
Min | Median | Max	0 | 14 | 384		0 | 17 | 266		1 | 16 | 266		
0–5	3982	16.0	383	9.9	280	11.5	.61
6–10	5344	21.5	759	19.6	485	20.0	
11–15	4193	16.9	644	16.6	393	16.2	
16–20	3102	12.5	512	13.2	322	13.3	
21–25	2190	8.8	375	9.7	217	8.9	
26–30	1558	6.3	325	8.4	194	8.0	
31–35	1135	4.6	212	5.5	131	5.4	
36+	3367	13.5	660	17.1	404	16.7	

aMOA, another mode of action; LOS, length of stay; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.
[a]For continuous variables, the *P*-value will be calculated using a Wilcoxon-Mann-Whitney test. For categorical variables, Fisher's exact test will be used.
[b]LOS in days only includes individuals with an inpatient stay.

Table 3. Comorbidities & Charlson Comorbidity Index by Type of Treatment Switch

Comorbidities	Overall		TNFi → TNFi		TNFi → aMOA		*P*-Value[a] (Between 2 subset)
	N	%	N	%	N	%	
Number of Patients (N)	24,871	100	3870	100	2426	100	
CCI Score Without Age and Rheumatic Disease	2.62 (1.90)		2.26 (1.74)		2.59 (1.87)		<.01
0	3091	12.4	626	16.2	291	12.0	
1	3884	15.6	716	18.5	388	16.0	
2	6017	24.2	1006	26.0	623	25.7	
3	5162	20.8	762	19.7	509	21.0	
4+	6717	27.0	760	19.6	615	25.4	
CCI Comorbidities							
Cancer	1063	4.3	159	4.1	135	5.6	.01
Cerebrovascular Disease	582	2.3	64	1.7	60	2.5	.03
Congestive Heart Failure	632	2.5	65	1.7	60	2.5	.03
Chronic Pulmonary Disease	3460	13.9	508	13.1	332	13.7	.54
Dementia	54	0.2	7	0.2	4	0.2	1
Diabetes Without Chronic Complication	3135	12.6	442	11.4	339	14.0	0
Diabetes With Chronic Complication	522	2.1	73	1.9	48	2.0	.85
Hemiplegia or Paraplegia	63	0.3	6	0.2	8	0.3	.17
HIV	15	0.1	2	0.1	1	0.04	1
Metastatic Solid Tumor	47	0.2	2	0.1	2	0.1	.64
Mild Liver Disease	1115	4.5	186	4.8	108	4.5	.54
Moderate or Severe Liver Disease	41	0.2	3	0.1	2	0.1	1
Moderate or Severe Renal Disease	791	3.2	87	2.3	76	3.1	.03
Myocardial Infarction	444	1.8	52	1.3	41	1.7	.28
Peripheral Vascular Disease	802	3.2	105	2.7	73	3.0	.48
Ulcer Disease	230	0.9	29	0.8	19	0.8	.88

aMOA, another mode of action; HIV, human immunodeficiency virus; CCI, Charlson Comorbidity Index; TNFi, tumor necrosis factor inhibitor.
[a]For continuous variables, the *P*-value was calculated using a Wilcoxon-Mann-Whitney test. For continuous variables, Fisher's exact test was used.

Table 4. Predictors of TNFi Cycling and Switching

Predictor	Description	SF[b] (%)	Min OR	Median OR	Max OR
Switching to aMoA	Cancer Chemotherapy	100	2.37	3.02	5.41
	CCI Score Without Rheumatic Disease	100	1.14	1.15	1.2
	CRP Test				
	CRP Abnormal[a] vs Normal	84.4	1.34	1.35	1.36
	CRP Not Performed vs Normal	84.4	1.42	1.48	1.49
TNFi Cycling	Psoriasis Diagnosis	99.2	0.28	0.29	0.3
	Other Diagnostic Radiology Procedures and Related Techniques	18.0	0.76	0.79	0.81
	Ophthalmologic and Otologic Conditions and Treatments	13.3	0.64	0.67	0.7
	Skin Disorders (Other Than Psoriasis)	8.6	0.73	0.74	0.77
	Prophylactic Vaccinations and Inoculations	6.3	0.74	0.79	0.81
	Gender (Male vs Female)	6.3	0.82	0.83	0.84

aMOA, another mode of action; AUC, area under the curve; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; OR, odds ratio; SF, selection frequency; TNFi, tumor necrosis factor inhibitor.
OR >1 → switching, OR <1 → cycling; [a]CRP >10 abnormal.
Performance: AUC: 0.625.
[b]SF measures a variable's "importance" in making predictions. SF of 100% implies the variable was included in all 128 networks (models) in the ensemble.

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