

Background

- Rheumatoid arthritis (RA) symptoms are suspected to be linked with exposure to colder environments
- Previous studies on RA and seasonality have focused on RA activity; however, none assess medication adherence

Objective

- To assess the impact of seasonal changes on adherence among patients beginning subcutaneous or oral RA treatment

Methods

- This is a retrospective cohort study of adult RA patients in the US enrolled in a large health plan taking subcutaneous or oral RA medications between 3/1/19 and 2/28/21
- Patients were included if they were newly diagnosed with RA (ICD-10 codes M05.X and M06.X)
- Medication adherence was tracked for 12 months after starting therapy
- Medication classes included: Tumor necrosis factor alpha (TNF-α) inhibitors, Janus Kinase (JAK) inhibitors, Interleukin-6 (IL-6) inhibitors, a T-cell blocker, and folate analogs
- Medication history was stratified into meteorological seasons for the northern hemisphere: spring (3/1-5/31), summer (6/1-8/31), fall (9/1-11/30), and winter (12/1-2/28)
- Monthly medication adherence was measured using proportion of days covered (PDC) between the first and last fill of the year
- The effect of seasonality on monthly adherence was estimated using linear regression, controlling for age, gender, and other patient demographics
- Predicted PDC was calculated using resultant equations
- P-values < 0.05 were significant

Results

- A total of 3,710 patients were included; adherence was captured for 39,628 member-months
- The average age of the cohort was 56 years (standard deviation (sd) = 14); 2,797 (75%) identified as female
- The average monthly PDC was 0.84
- Predicted monthly PDC was highest in summer (0.85), followed by spring (0.85), fall (0.84), and lowest in the winter (0.83)
- Significant differences in PDC by season were found in winter (p<0.01)
- For TNF-α inhibitors, spring (p<0.01) and winter (p<0.01) were associated with lower mean PDCs
- None of the season coefficients were statistically significant for JAK inhibitors
- Adherence for IL-6 inhibitors (p=0.04), T-Cell blockers (p<0.01) and folate analog (p=0.01) were the most sensitive to winter seasonal changes
- Subsampling by climate region revealed the negative impact of winter on medication adherence was limited to members residing in humid (p=0.00) or cold climates (p=0.01)

Conclusions

- Medication adherence decreased in winter months, but the effect of seasonality depended on class and was drug specific
- Seasonality influences adherence, but only for specific seasons

Table 1: Cohort description

Variable	Value
Number of patients	3,710
Age, Mean (SD)	56 (14)
Gender, n(%)	
Male	913 (25%)
Female	2,797 (75%)
Insurance type, n (%)	
Commercial	2,493 (67%)
Medicare	1,217 (33%)
Months to initiate therapy after diagnosis, Mean (SD)	3.8 (5.5)
Non-RA medication fills, Mean (SD)	11.3 (9.6)
Number of Comorbidities, Mean (SD)	2.3 (1.6)
Monthly PDC, Mean (SD)	0.84 (0.19)
Adherent, n (%)	2,344 (63%)

Figure 1: Predicted PDC by Season

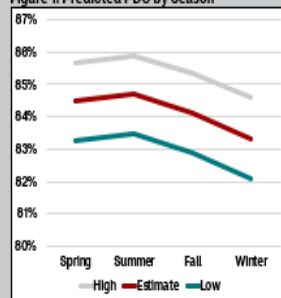


Table 2: Linear regression results for PDC

Variable	Coefficient (95% CI)	P-value
Season		
Fall	(reference)	
Spring	-0.01 (-0.02, 0)	0.081
Summer	0 (-0.01, 0.01)	0.9
Winter	-0.02 (-0.03, -0.01)	<0.001
Gender		
Female	(reference)	
Male	0.02 (0.01, 0.03)	<0.001
Age		
18-44	(reference)	
45-54	0.02 (0.01, 0.03)	<0.001
55-64	0.03 (0.02, 0.04)	<0.001
65-74	0.07 (0.05, 0.08)	<0.001
≥75	0.08 (0.06, 0.09)	<0.001
Insurance type		
Commercial	(reference)	
Medicare	-0.04 (-0.05, -0.03)	<0.001
Months post-diagnosis	-0.01 (-0.01, 0.00)	<0.001
Comorbidities	0 (0, 0)	<0.001
Non-RA fills	0 (0, 0)	<0.001
Out of pocket expenses	0 (0, 0)	<0.001
Year		
2019	(reference)	
2020	0.01 (0, 0.02)	0.053
2021	0.03 (0.02, 0.04)	<0.001
2022	0.05 (0.03, 0.07)	<0.001

Table 3: Linear regression models stratified by drug class

Variable	TNF		JAK Inhibitor		IL-6 Inhibitor		T-Cell Blocker		Folate Analog	
	Beta	P-Value	Beta	P-Value	Beta	P-Value	Beta	P-Value	Beta	P-Value
Season										
Fall	Reference		Reference		Reference		Reference		Reference	
Spring	-0.04 <0.001		-0.02 0.20		0.01 >0.9		-0.07 0.04		0.00 0.80	
Summer	-0.01 0.20		-0.02 0.20		0.01 0.90		-0.02 0.50		0.00 0.50	
Winter	-0.03 <0.001		-0.02 0.30		-0.14 0.04		-0.11 <0.001		-0.02 0.01	
Male Gender	0.02 <0.001		0.03 0.09		0.10 0.15		-0.04 0.20		0.02 <0.001	
Age										
18-44	Reference		Reference		Reference		Reference		Reference	
45-54	0.03 <0.001		0.06 <0.001		-0.06 0.40		0.03 0.30		0.02 0.01	
55-64	0.02 0.00		0.09 <0.001		0.04 0.50		0.05 0.10		0.03 <0.001	
65-74	0.02 0.20		0.11 <0.001		-0.33 0.20		-0.05 0.30		0.09 <0.001	
≥75	0.00 >0.9		0.09 0.01		0.12 0.03		0.10 >0.001			
Medicare Insurance	0.01 0.30		-0.04 0.06				-0.02 0.50		-0.04 <0.001	
Months post-diagnosis	0.00 <0.001		0.00 0.12		0.00 0.40		0.00 0.60		-0.01 <0.001	
Comorbidities	0.00 0.02		0.00 >0.9		0.01 0.40		0.00 0.90		0.01 <0.001	
Non-RA fills	0.00 <0.001		0.00 <0.001		0.00 0.11		0.00 0.00		0.00 <0.001	
Out of pocket expenses	0.00 <0.001		0.00 0.30		0.00 0.80		0.00 0.40		0.00 <0.001	
Year										
2019	Reference		Reference		Reference		Reference		Reference	
2020	0.04 <0.001		0.03 0.20		0.06 0.50		-0.01 0.80		0.01 0.01	
2021	0.06 <0.001		0.03 0.20		0.04 0.70		0.01 0.90		0.03 <0.001	
2022	0.10 <0.001		0.01 0.70		0.07 0.60		-0.11 0.09		0.06 <0.001	

TNF: Tumor necrosis factor; JAK: Janus Kinase; RA: Rheumatoid Arthritis; Beta: Linear regression coefficient

Figure 2: Predicted PDC by Season and drug class

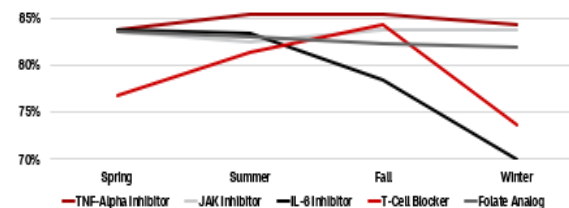


Table 4: Linear regression models stratified by region climate type

Variable	Dry		Humid		Cold		Marine	
	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
Season								
Fall	(reference)		(reference)		(reference)		(reference)	
Spring	-0.02 (-0.06, 0.01)	0.2	0 (-0.02, 0.02)	>0.9	-0.01 (-0.02, 0.00)	0.057	0.03 (-0.02, 0.08)	0.2
Summer	-0.02 (-0.06, 0.01)	0.14	0 (-0.01, 0.02)	0.6	0 (-0.01, 0.01)	>0.9	0.03 (-0.02, 0.08)	0.3
Winter	-0.02 (-0.05, 0.02)	0.3	-0.02 (-0.04, -0.01)	0.004	-0.02 (-0.03, 0.00)	0.006	0.02 (-0.03, 0.07)	0.5
Male Gender	0.02 (-0.01, 0.05)	0.2	0.02 (0.00, 0.03)	0.005	0.02 (0.01, 0.03)	<0.001	0.05 (0.00, 0.09)	0.034
Age								
18-44	(reference)		(reference)		(reference)		(reference)	
45-54	0 (-0.03, 0.03)	>0.9	0.03 (0.01, 0.05)	0.001	0.02 (0.01, 0.04)	<0.001	-0.02 (-0.07, 0.02)	0.4
55-64	0.03 (0.00, 0.05)	0.08	0.04 (0.02, 0.05)	<0.001	0.03 (0.01, 0.04)	<0.001	0.05 (0.00, 0.10)	0.064
65-74	0.04 (-0.03, 0.10)	0.3	0.08 (0.05, 0.10)	<0.001	0.06 (0.04, 0.08)	<0.001	0.12 (0.02, 0.22)	0.017
≥75	0.09 (0.01, 0.17)	0.03	0.07 (0.04, 0.10)	<0.001	0.08 (0.06, 0.10)	<0.001	0.2 (0.05, 0.34)	0.008
Medicare Insurance	-0.02 (-0.07, 0.04)	0.6	-0.03 (-0.05, -0.01)	0.002	-0.05 (-0.06, -0.03)	<0.001	-0.09 (-0.18, 0.00)	0.047
Months post-diagnosis	-0.01 (-0.01, 0.00)	<0.001	-0.01 (-0.01, 0.00)	<0.001	-0.01 (-0.01, 0.00)	<0.001	-0.01 (-0.01, 0.00)	0.003
Comorbidities	0.01 (0.00, 0.01)	0.41	0.01 (0.00, 0.01)	0.63	0.01 (0.00, 0.01)	<0.001	0.01 (-0.01, 0.01)	0.9
Non-RA fills	0 (0.00, 0.00)	<0.001	0 (0.00, 0.00)	<0.001	0 (0.00, 0.00)	<0.001	0 (0.00, 0.00)	0.4
Out of pocket expenses	0 (0.00, 0.00)	<0.001	0 (0.00, 0.00)	<0.001	0 (0.00, 0.00)	<0.001	0 (0.00, 0.00)	0.4
Year								
2019	(reference)		(reference)		(reference)		(reference)	
2020	0.04 (0.01, 0.08)	0.019	0.02 (0.00, 0.03)	0.027	0.01 (-0.01, 0.02)	0.3	-0.07 (-0.12, -0.02)	0.007
2021	0.05 (0.00, 0.09)	0.033	0.02 (0.01, 0.04)	0.01	0.03 (0.02, 0.04)	<0.001	-0.05 (-0.11, 0.02)	0.14
2022	0.06 (-0.02, 0.14)	0.14	0.03 (-0.01, 0.06)	0.2	0.08 (0.03, 0.09)	<0.001	0.01 (-0.11, 0.13)	0.9

RA: Rheumatoid Arthritis; Beta: Linear regression coefficient; 95% CI: 95% confidence interval; p: p-value

Figure 3: Predicted PDC by Season and region climate

