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Risk of Cardiovascular Events, Cancer, and All-Cause Mortality in JAK Inhibitors Compared to TNF Inhibitors: Analysis of a Large Real-World Claims Database

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Background

Tofacitinib was the first Janus kinase inhibitor approved for rheumatoid arthritis (RA). Concerns about the safety of JAK inhibitors, particularly in terms of cardiovascular events, cancer, and all-cause mortality, have emerged over time.(1)

The ORAL Surveillance trial, a large, post-marketing study mandated by the FDA, evaluated tofacitinib's safety compared to TNF inhibitors in RA patients. The trial revealed increased risks of major cardiovascular adverse events (MACE), cancer, and mortality, especially at the higher dose of 10 mg.(2) In response, the FDA extended safety warnings across the entire JAK inhibitor class.(3)

Objective

This study aims to provide further insights into the safety concerns raised by the ORAL Surveillance trial while broadening the analysis to include other JAK inhibitors and immune-related diseases beyond RA.

Using a large claims database, we will assess real-world safety outcomes - including all-cause mortality, major cardiovascular adverse events (MACE), and cancer incidence - comparing tofacitinib and other JAK inhibitors to TNF inhibitors in patients with immune-mediated diseases.

Methods

Patients initiating JAKis or TNFis for an immune-mediated condition between 2018–2022 were identified from Oracle Life Sciences' US Claims database. Propensity-Score Matching was performed to match JAKis and tofacitinib users to TNFis users.

All-cause mortality, cardiovascular mortality, MACE, and cancers were investigated during follow-up. Kaplan-Meier (KM) analysis was performed, incidence of events was compared among treatment groups using the log-rank test. Hazard ratios (HRs) were estimated via multivariate Cox regression models.

Results

We identified 23,255 patients initiating JAKis (12,707 received tofacitinib), and 138,826 TNFis. Mean (SD) age was 49.8 (15.9), 51.1 (15.5) and 46.1 (14.4) respectively. 20,576 JAKis and 12,458 tofacitinib users were matched 1:1 to TNFis patients.

Table 1. Patients' baseline characteristics

Variable	Statistics	Total	JAK inhibitors	Tofacitinib	Anti-TNFs
		N = 162,081	N = 23,255	N = 12,707	N = 138,826
Age	Mean (SD)	46.63 (14.70)	49.78 (15.91)	51.06 (15.47)	46.11 (14.42)
	Median	48	52	53	47
	Q1 - Q3	[36.00 ; 57.00]	[40.00 ; 60.00]	[43.00 ; 60.00]	[36.00 ; 57.00]
Gender	Female	107710 (66.45%)	17089 (73.49%)	9591 (75.48%)	90621 (65.28%)
	Male	54371 (33.55%)	6166 (26.51%)	3116 (24.52%)	48205 (34.72%)
Race/ Ethnicity	White	58516 (36.10%)	7669 (32.98%)	4133 (32.53%)	50847 (36.63%)
	Hispanic or Latino	15480 (9.55%)	2447 (10.52%)	1196 (9.41%)	13033 (9.39%)
	Black or African American	10534 (6.50%)	1552 (6.67%)	759 (5.97%)	8982 (6.47%)
	Asian or Pacific Islander	4635 (2.86%)	1018 (4.38%)	381 (3.00%)	3617 (2.61%)
	Some Other race	9442 (5.83%)	1466 (6.30%)	759 (5.97%)	7976 (5.75%)
	Unknown	63474 (39.16%)	9103 (39.14%)	5479 (43.12%)	54371 (39.16%)
CV risk factors					
Diabetes without chronic complications		15192 (9.37%)	2072 (8.91%)	1129 (8.88%)	13120 (9.45%)
Diabetes with chronic complication		8723 (5.38%)	1338 (5.75%)	796 (6.26%)	7385 (5.32%)
Primary hypertension		55773 (34.41%)	8475 (36.44%)	4833 (38.03%)	47298 (34.07%)
Other hypertensive disease		6257 (3.86%)	1173 (5.04%)	669 (5.26%)	5084 (3.66%)
Hypercholesterolemia		12093 (7.46%)	2008 (8.63%)	1132 (8.91%)	10085 (7.26%)
Smoking		41164 (25.40%)	4911 (21.12%)	2831 (22.28%)	36253 (26.11%)
Obesity		37913 (23.39%)	5136 (22.09%)	2889 (22.74%)	32777 (23.61%)
Other Comorbidities					
Myocardial infarction		2348 (1.45%)	383 (1.65%)	223 (1.75%)	1965 (1.42%)
Congestive heart failure		4356 (2.69%)	861 (3.70%)	525 (4.13%)	3495 (2.52%)
Peripheral vascular disease		7203 (4.44%)	1326 (5.70%)	757 (5.96%)	5877 (4.23%)
Cerebrovascular disease		4424 (2.73%)	776 (3.34%)	440 (3.46%)	3648 (2.63%)
Chronic pulmonary disease		28669 (17.69%)	4570 (19.65%)	2546 (20.04%)	24099 (17.36%)
Peptic ulcer disease		2764 (1.71%)	288 (1.24%)	168 (1.32%)	2476 (1.78%)
Mild liver disease		13815 (8.52%)	1736 (7.47%)	945 (7.44%)	12079 (8.70%)
Moderate severe liver disease		574 (0.35%)	65 (0.28%)	27 (0.21%)	509 (0.37%)
Mild moderate renal disease		5933 (3.66%)	1070 (4.60%)	659 (5.19%)	4863 (3.50%)
Severe renal disease		626 (0.39%)	86 (0.37%)	52 (0.41%)	540 (0.39%)
HIV		352 (0.22%)	35 (0.15%)	15 (0.12%)	317 (0.23%)
Hemiplegia		677 (0.42%)	100 (0.43%)	58 (0.46%)	577 (0.42%)
Dementia		881 (0.54%)	160 (0.69%)	89 (0.70%)	721 (0.52%)
Depression		32784 (20.23%)	4468 (19.21%)	2539 (19.98%)	28316 (20.40%)

KM curves showed significantly higher probabilities of all-cause mortality in the JAKis (Log-Rank p<0.0001) and tofacitinib subgroups (Log-Rank p=0.0011) compared to TNFis treatment group (Figure 1). KM curves also showed significantly higher incidence of cardiovascular mortality (not shown), and newly diagnosed cancer (Figure 3) for JAKis and tofacitinib compared to TNFis (Log-Rank p<0.05).

Based on a multivariate Cox model (Table 2), JAKis were associated with a significantly higher risk of all-cause mortality (HR=1.388 [1.199 ; 1.606] , p<0.0001), CV mortality (HR=1.623 [1.166 ; 2.259], p=0.0041) and cancer (HR=1.213 [1.104 ; 1.334], p<0.0001) compared to TNFis. Tofacitinib was associated with a significantly higher risk of all-cause mortality (HR=1.301 [1.089 ; 1.555], p=0.0038) and CV mortality (HR=1.625 [1.071 ; 2.465], p=0.0225) compared to TNFis.

Neither the KM analyses or the Cox regression models showed a significant difference in the incidence of MACE in the tofacitinib and JAKis treatment groups compared to the TNFis group.

Table 2. Multivariate analysis of the Incidence of mortality, MACE and cancer

Model[1]	Outcome		Hazard Ratio	95% Confidence Interval	P-value
1	All-cause mortality	JAKis vs. TNFis	1.388	[1.199 ; 1.606]	<0.0001
2		Tofacitinib vs. TNFis	1.301	[1.089 ; 1.555]	0.0038
3	CV mortality	JAKis vs. TNFis	1.623	[1.166 ; 2.259]	0.0041
4		Tofacitinib vs. TNFis	1.625	[1.071 ; 2.465]	0.0225
5	MACE	JAKis vs. TNFis	1.07	[0.988 ; 1.159]	0.0984
6		Tofacitinib vs. TNFis	1.051	[0.951 ; 1.161]	0.3301
7	Cancer	JAKis vs. TNFis	1.213	[1.104 ; 1.334]	<0.0001
8		Tofacitinib vs. TNFis	1.102	[0.981 ; 1.238]	0.1031

Figure 1. All-cause mortality in JAKis and tofacitinib vs. TNFis, KM analysis

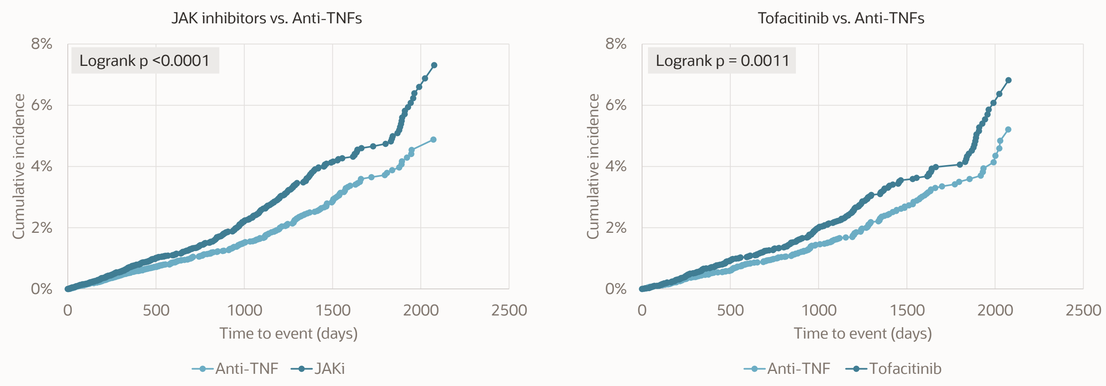


Figure 2. Incidence of MACE[2] in JAKis and tofacitinib vs. TNFis, KM analysis

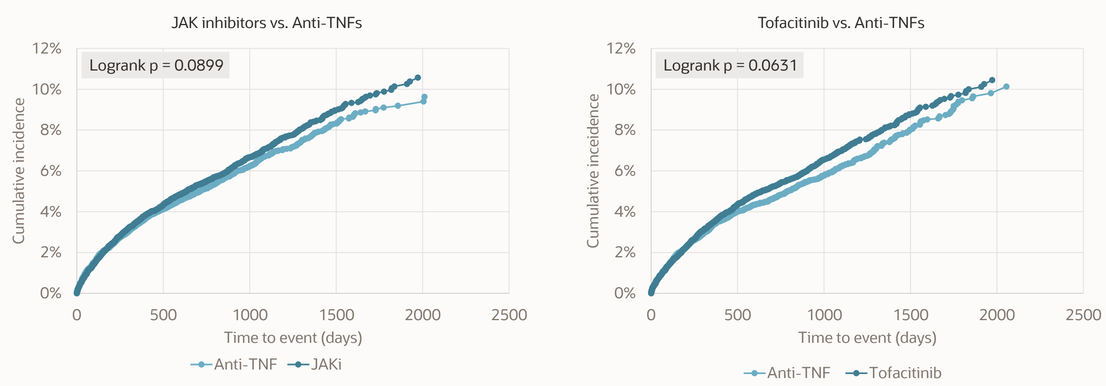
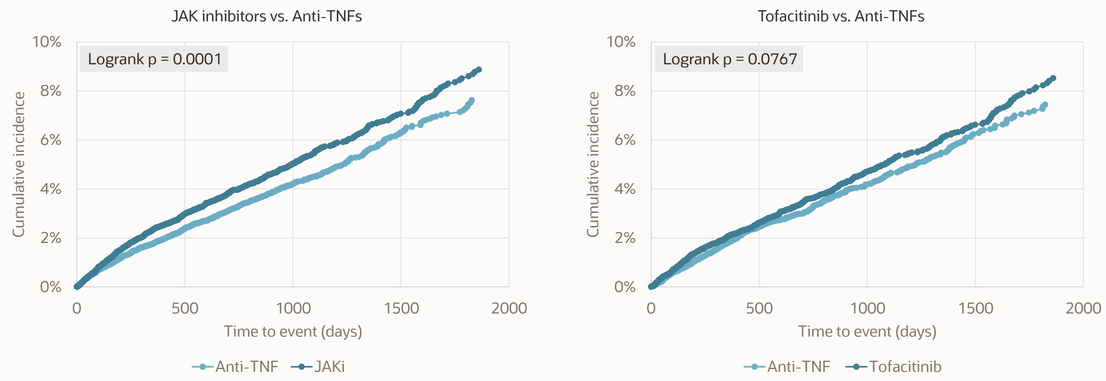


Figure 3. Incidence of cancer[3] in JAKis and tofacitinib vs. TNFis, KM analysis



Abbreviations: JAKis: Janus kinase inhibitors; TNFis: Tumor Necrosis Factor inhibitors; CV: Cardiovascular; KM: Kaplan-Meier;
[1] Multivariate proportional hazards Cox models adjusted on baseline demographics and clinical characteristics
[2] MACE: Major Cardiovascular Events defined as non-fatal stroke, acute myocardial infarction or CV death
[3] Any cancer except non-melanoma skin cancer

Conclusion

Based on an analysis of a large secondary claims database, patients initiating JAK inhibitors had a higher risk of all-cause mortality, cardiovascular mortality, and newly diagnosed cancers compared to those treated with TNF inhibitors. For tofacitinib users, the risks of all-cause and cardiovascular mortality were significantly higher than for TNF inhibitor users, aligning with findings from the ORAL Surveillance trial, though no significant increase in cancer risk was observed. There was no significant difference in the risk of MACE between treatment groups.

References

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