Malignancies risk in rheumatoid arthritis patients treated with tofacitinib or TNF inhibitors, a national study: RELATION study

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Authors, we would be grateful if you could provide the department for your affiliation. Thank you.

Introduction

➤ Patients with IMID, including those with RA, are at increased risk of cancer compared with the general population.[1-3]

➤ In the ORAL Surveillance trial, which included patients with RA aged ≥50 years who had ≥1 additional CV risk factor, the risk of malignancies (excluding NMSC) was higher among patients receiving tofacitinib vs TNFi at the overall study population level.[4]

Objective

➤ To assess the impact of tofacitinib and TNFi on the risk of malignancies in patients with RA treated in real-world clinical practice.

Methods

Study design and patients

➤ The RELATION study is a retrospective, observational cohort study using the French national healthcare database (ie the SNDS).

➤ Patients were aged ≥18 years, were affiliated with the French national health insurance scheme, had a diagnosis of RA, and had initiated tofacitinib after 1 November 2017, or a TNFi (ie adalimumab, etanercept or other TNFi) after 1 January 2010 (the index date), without having previous exposure to tofacitinib or the index TNFi.

➤ Patients were excluded if they had a history of malignancy (excluding NMSC) in the 4 years preceding the index date.

➤ The follow-up period was from treatment initiation until death, loss to follow-up, treatment discontinuation or 31 December 2020, whichever occurred first.

Outcomes

➤ Malignancies (excluding NMSC) were defined as the first hospitalisation with an ICD-10 code for malignancy during the follow-up period.
– Events were identified until 90 days after treatment discontinuation.

Statistical analyses

➤ Further to the development of the abstract, 1:3 PS matching was conducted to balance the baseline characteristics of patients initiating tofacitinib or TNFi; these data are reported here.

➤ Crude IRs of malignancies (excluding NMSC) were reported along with two-sided 95% CIs, which were calculated using the exact Poisson distribution.

➤ Cox proportional hazards regression models were used to compare the risk of malignancies with tofacitinib vs TNFi during the follow-up period.

➤ Subgroup analyses were done according to age (<50 years; ≥50 to <65 years; ≥65 years)

➤ Sensitivity analyses were performed by:
– Applying a remanence period of 1-year post-bDMARD or post-tsDMARD treatment discontinuation
– Excluding patients with a malignancy within 1 year after the index date
– Excluding patients with a malignancy within 90 days after the index date.

Results

Patients

➤ In total, 2811 patients initiated tofacitinib and 36 767 initiated TNFi (adalimumab, n=10 621; etanercept, n=16 512; other TNFi, n=9634).

➤ After PS matching, the tofacitinib cohort included 2628 patients and the TNFi cohort included 7884 patients.

➤ Patient characteristics were well balanced in the PS-matched cohorts (**Table**).

Table. Patient characteristics

	Tofacitinib (N=2628)	TNFi (N=7884)
Demographics		
Age[a] (years), mean (SD)	56.2 (12.9)	56.0 (13.5)
Female, n (%)	2101 (79.9)	6257 (79.4)
RA-related characteristics		
Time since first available RA information[a] (years), mean (SD)	2.4 (1.3)	2.4 (1.3)
Non-bDMARD use,[b] n (%)		
Glucocorticoids	1294 (49.2)	3935 (49.9)
Leflunomide	313 (11.9)	963 (12.2)
Methotrexate	1437 (54.7)	4323 (54.8)
NSAIDs	532 (20.2)	1585 (20.1)
Sulfasalazine	78 (3.0)	231 (2.9)
CV risk factor (any),[c] n (%)	1716 (65.3)	5147 (65.3)
Alcohol use disorders	29 (1.1)	95 (1.2)
Atherosclerosis	12 (0.5)	43 (0.6)
Diabetes	242 (9.2)	744 (9.4)
Dyslipidaemia	533 (20.3)	1605 (20.4)
Hypertension	1028 (39.1)	3110 (39.5)
Oral contraceptives	367 (13.4)	1051 (13.3)
Severe obesity	285 (10.8)	873 (11.1)
Smoking	256 (9.7)	798 (10.1)
Other comorbidities,[c] n (%)		
Chronic respiratory disease	114 (4.3)	379 (4.8)
Cirrhosis and portal hypertension	3 (0.1)	22 (0.3)
Inflammatory bowel disease	29 (1.1)	109 (1.4)
Severe kidney disease	10 (0.4)	7 (0.1)

[a]At the index date
[b]≤6 months pre-index date
[c]Comorbidities and traditional CV risk factors were identified based on hospitalisations, procedures or medication dispensing in the 4 years prior to cohort entry

Figure 1. Crude IRs (95% CIs) of malignancies per 1000 PY of follow-up among matched tofacitinib and TNFi populations
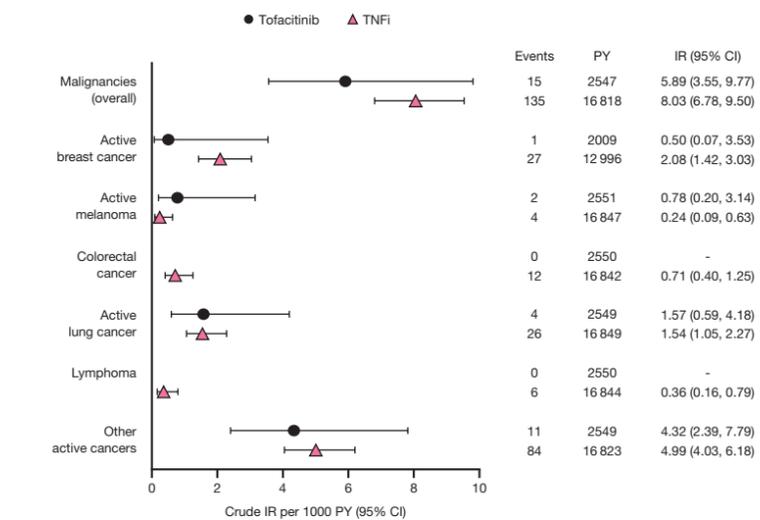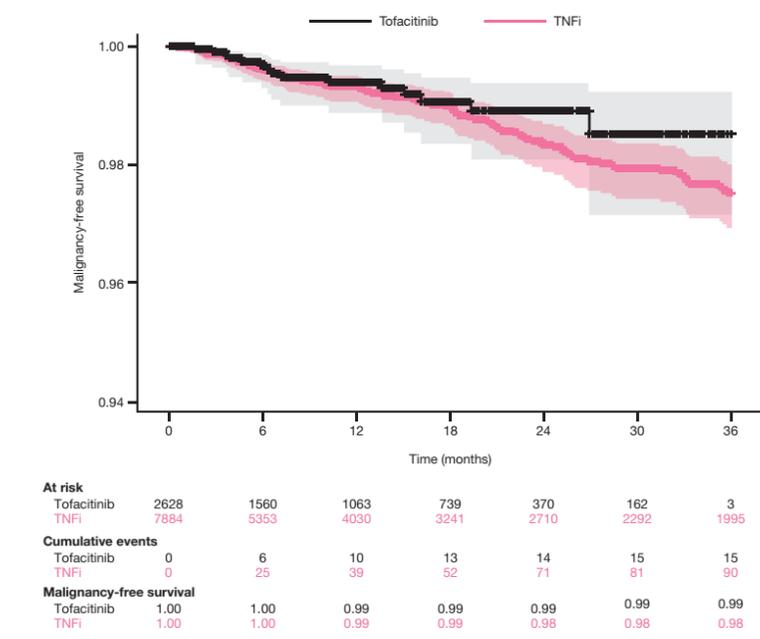

	Events	PY	IR (95% CI)
Malignancies (overall)	15	2547	5.89 (3.55, 9.77)
	135	16 818	8.03 (6.78, 9.50)
Active breast cancer	1	2009	0.50 (0.07, 3.53)
	27	12 996	2.08 (1.42, 3.03)
Active melanoma	2	2551	0.78 (0.20, 3.14)
	4	16 847	0.24 (0.09, 0.63)
Colorectal cancer	0	2550	-
	12	16 842	0.71 (0.40, 1.25)
Active lung cancer	4	2549	1.57 (0.59, 4.18)
	26	16 849	1.54 (1.05, 2.27)
Lymphoma	0	2550	-
	6	16 844	0.36 (0.16, 0.79)
Other active cancers	11	2549	4.32 (2.39, 7.79)
	84	16 823	4.99 (4.03, 6.18)

Figure 2. Malignancy-free survival among matched patients who initiated tofacitinib or TNFi

At risk							
Tofacitinib	2628	1560	1063	739	370	162	3
TNFi	7884	5353	4030	3241	2710	2292	1995
Cumulative events							
Tofacitinib	0	6	10	13	14	15	15
TNFi	0	25	39	52	71	81	90
Malignancy-free survival							
Tofacitinib	1.00	1.00	0.99	0.99	0.99	0.99	0.99
TNFi	1.00	1.00	0.99	0.99	0.98	0.98	0.98

Conclusions

➤ In this large, population-based study, tofacitinib was not associated with an increased risk of malignancies (excluding NMSC) in comparison with TNFi in patients with RA treated in real-world settings.

➤ Studies with longer follow-up durations may be necessary to understand the long-term implications of tofacitinib vs TNFi on the risk of malignancies.

Risk of malignancies

➤ Over a median follow-up period of 11.31 months (tofacitinib, 8.56 months; TNFi, 12.52 months), crude IRs of malignancies among matched populations were similar with tofacitinib vs TNFi (**Figure 1**).
– No events of colorectal cancer or lymphoma were reported with tofacitinib.

➤ Malignancy-free survival over time was similar with tofacitinib vs TNFi (**Figure 2**).

➤ The risk of malignancies was similar with tofacitinib vs TNFi (adjusted HR 0.76 [95% CI 0.44, 1.32]; p=0.3347).
– Similar results were found for other active cancers (HR 0.97 [95% CI 0.50, 1.89]; p=0.9382).
– For other specific cancer types, the number of events was too low to perform these analyses.

Subgroup and sensitivity analyses

➤ The risk of malignancies was not significantly different between tofacitinib and TNFi across age subgroups (data not shown).

➤ No difference in the risk of malignancies with tofacitinib vs TNFi was observed in the various sensitivity analyses (data not shown).

Limitations

➤ Unobserved confounders may not be ruled out. However, both cohorts were well balanced after PS matching, so minimal bias should arise from observed confounders.

➤ Median follow-up time was relatively short in the tofacitinib cohort (<1 year), so the long-term implications of tofacitinib vs TNFi on the risk of malignancies remain unclear.

➤ Despite their wealth of data, administrative databases may contain inaccuracies and omissions. However, this limitation should equally impact both cohorts, and hence minimally impact cohort comparisons.

References

1. Smitten AL et al. Arthritis Res Ther 2008; 10: R45.
2. Simon TA et al. Arthritis Res Ther 2015; 17: 212.
3. He MM et al. JAMA Oncol 2022; 8: 209–219.
4. Ytterberg SR et al. N Engl J Med 2022; 386: 316–326.
5. DeTora LM et al. Ann Intern Med 2022; 175: 1298–1304.
6. Gottenberg JE et al. Arthritis Rheumatol 2022; 74 (Suppl 9): Abstract 1984.