Acute cardiovascular events risk in rheumatoid arthritis patients treated with tofacitinib or TNF inhibitors, a nationwide cohort study: RELATION study

J-E Gottenberg,[1] N Mammar,[2] M Kessouri,[2] J Rudant,[2] N Assi,[3] B Grenier,[3] J Kirchgesner[4]

[1]Hautepierre Hospital, Strasbourg, France; [2]Pfizer France, Paris, France; [3]Heva, Lyon, France; [4]Saint-Antoine Hospital, Paris, France

1429

Introduction

- Patients with RA are at increased risk of MACE compared with the general population.[1,2]
- In the ORAL Surveillance trial, which included patients with RA aged ≥50 years who had ≥1 additional CV risk factor, the risk of MACE was higher among patients receiving tofacitinib vs TNFi at the overall study population level.[3]

Objective

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

Methods

Study design and patients

- The RELATION study is a retrospective observational cohort study that used the French national healthcare database (SNDS).
- Patients were aged ≥18 years, were affiliated with the French national health insurance scheme, had a diagnosis of RA, and initiated tofacitinib after November 1, 2017, or a TNFi (ie, adalimumab, etanercept, or other TNFi) after January 1, 2010 (the index date) without having previous exposure to tofacitinib or the index TNFi.
- Patients were excluded if they had a history of MACE 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 December 31, 2020, whichever occurred first.

Outcomes

- MACE (excluding CV death) was defined as the first hospitalization with an ICD-10 code or medical procedure code for MACE during the follow-up period.
  - The following types of MACE were assessed:
    - Ischemic heart disease (including MI)
    - Cerebrovascular disease (including stroke)
    - Peripheral artery disease
  - Events were identified until 60 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 MACE (excluding CV death) 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 MACE with tofacitinib vs TNFi during the follow-up period.
- Subgroup analyses were done according to age (ie, <50 years, ≥50 to <65 years, or ≥65 years)
- A sensitivity analysis was performed in which patients were excluded if they experienced a MACE within 60 days after the index date.

Results

Patients

- In total, 2,811 patients initiated tofacitinib and 36,767 initiated TNFi (adalimumab, n=10,621; etanercept, n=16,512; other TNFi, n=9,634).
- After PS matching, the tofacitinib cohort included 2,628 patients and the TNFi cohort included 7,884 patients.
- Patient characteristics were well balanced in the PS-matched cohorts (**Table**).

Table. Patient characteristics

	Tofacitinib (N=2,628)	TNFi (N=7,884)
Demographics		
Age[a], years, mean (SD)	56.2 (12.9)	56.0 (13.5)
Female, n (%)	2,101 (79.9)	6,257 (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	1,294 (49.2)	3,935 (49.9)
Leflunomide	313 (11.9)	963 (12.2)
Methotrexate	1,437 (54.7)	4,323 (54.8)
NSAIDs	532 (20.2)	1,585 (20.1)
Sulfasalazine	78 (3.0)	231 (2.9)
CV risk factor (any)[c], n (%)	1,716 (65.3)	5,147 (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)
Dyslipidemia	533 (20.3)	1,605 (20.4)
Hypertension	1,028 (39.1)	3,110 (39.5)
Oral contraceptives	367 (13.4)	1,051 (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 hospitalizations, procedures, or medication dispensing in the 4 years prior to cohort entry

Figure 1. Crude IRs (95% CIs) of MACE per 1,000 PY of follow-up among matched tofacitinib and TNFi cohorts

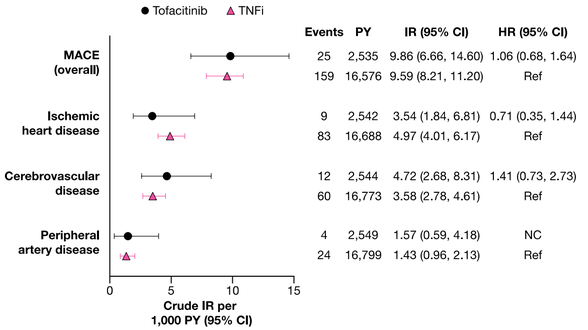
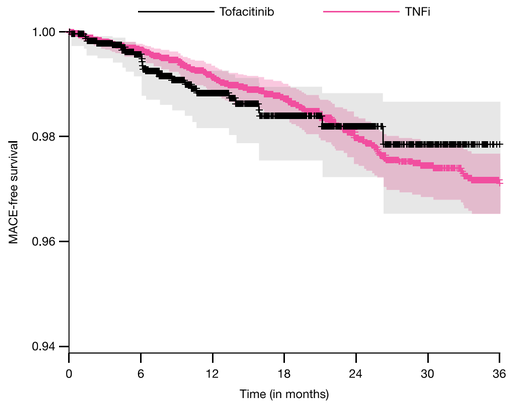


Figure 2. MACE-free survival among patients who initiated tofacitinib or TNFi



At risk							
Tofacitinib	2,628	1,557	1,054	730	368	158	3
TNFi	7,884	5,347	4,008	3,221	2,678	2,254	1,959
Cumulative events							
Tofacitinib	0	9	19	23	24	25	25
TNFi	0	23	47	62	84	98	105
MACE-free survival							
Tofacitinib	1.00	1.00	0.99	0.98	0.98	0.98	0.98
TNFi	1.00	1.00	0.99	0.99	0.98	0.97	0.97

Conclusions

- **In this large population-based study, tofacitinib was not associated with an increased risk of MACE 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 MACE.**

Risk of MACE

- Over a median follow-up period of 11.21 months (tofacitinib: 8.54 months, TNFi: 12.43 months), crude IRs of MACE were similar with tofacitinib vs TNFi (**Figure 1**).
- MACE-free survival over time was similar with tofacitinib vs TNFi (**Figure 2**).
- The risk of MACE (overall) was similar with tofacitinib vs TNFi (adjusted HR 1.06 [95% CI 0.68, 1.64]; p=0.8127) (**Figure 1**).
  - Similar results were found for ischemic heart disease (HR 0.71 [95% CI 0.35, 1.44]; p=0.3433) and cerebrovascular disease (HR 1.41 [95% CI 0.73, 2.73]; p=0.3116).
  - For peripheral artery disease, the number of events was too low to perform these analyses.

Subgroup and sensitivity analyses

- The risk of MACE was not significantly different between tofacitinib and TNFi across age subgroups (data not shown).
- No difference in the risk of MACE with tofacitinib vs TNFi was observed in the sensitivity analysis that excluded patients who experienced a MACE within 60 days after the index date (data not shown).

Limitations

- Unobserved confounders may not be ruled out; however, both cohorts were well balanced after PS matching, therefore minimal bias should arise from observed confounders.
- Median follow-up time was relatively short in the tofacitinib cohort (ie, <1 year), so long-term implications of tofacitinib vs TNFi on MACE risk 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.
- In ORAL Surveillance, excess risk of MACE with tofacitinib vs TNFi was primarily observed in patients with a history of ASCVD (including coronary artery disease, cerebrovascular disease, and peripheral artery disease).[4] Exclusion of some patients with a history of ASCVD from this analysis may impact the ability to detect an excess risk of MACE with tofacitinib vs TNFi.

Abbreviations

ASCVD, atherosclerotic cardiovascular disease; **bDMARD**, biologic DMARD; **CI**, confidence interval; **CV**, cardiovascular; **HR**, hazard ratio; **ICD-10**, International Classification of Diseases, 10th Revision; **IR**, incidence rate; **MACE**, major adverse cardiovascular event(s); **MI**, myocardial infarction; **N**, number of evaluable patients; **n**, number of patients with characteristics; **NC**, not calculated; **PS**, propensity score; **PY**, patient-years; **Ref**, reference group; **SD**, standard deviation; **SNDS**, Système National des Données de Santé; **TNFi**, TNF inhibitor(s).

References

1. Aviña-Zubieta JA et al. Ann Rheum Dis 2012; 71: 1524-1529.
2. Turesson C et al. Ann Rheum Dis 2004; 63: 952-955.
3. Ytterberg SR et al. N Engl J Med 2022; 386: 316-326.
4. Charles-Schoeman C et al. Ann Rheum Dis 2022; epub ahead of print (doi: 10.1136/ard-2022-222259).

Acknowledgments

The authors thank the Direction de la stratégie, des études et des statistiques (DSES), Département Accès, Traitement et Analyse de la Donnée (DATAD), and Demandes Externes (DEMEX) teams at the Caisse nationale de l'assurance maladie (CNAM) for the data extraction.

This study was sponsored by Pfizer Inc. Medical writing support, under the direction of the authors, was provided by Samuel Rochette, MSc, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer Inc, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (Ann Intern Med 2022; 175: 1298-1304).

References to other presentations

Analyses of the risk of malignancies in the RELATION study are reported in Poster 1984.

Disclosure of interest

JE Gottenberg has received grants and/or research support from Bristol-Myers Squibb and Pfizer Inc, has acted as a consultant for AbbVie, Bristol-Myers Squibb, Eli Lilly, Galapagos, Gilead Sciences, MSD, and Pfizer Inc, and has acted as an advisor or review panel member for Novartis. N Mammar, M Kessouri, and J Rudant are employees and stockholders of Pfizer Inc. N Assi and B Grenier are employees of Heva. J Kirchgesner has acted as a consultant for Gilead Sciences, Pfizer Inc, and Roche, has been a member of speakers' bureau and symposia for Pfizer Inc, and has acted as an expert witness for Pfizer Inc.

Poster presented at ACR Convergence 2022