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Disease-modifying Drugs (DMARDs), Rheumatoid arthritis, Malignancy

Incident malignancies in patients with rheumatoid arthritis in daily rheumatological care

Martin Schaefer*[1], Yvette Meissner[1], Bernhard Manger[2], Sylvia Berger[3], Karin Rockwitz[4], Anne Regierer[1], Anja Strangfeld[1, 5]

[1]German Rheumatism Research Centre Berlin, Epidemiology and Health Services Research, Berlin, Germany, *[2]Universitätsklinikum Erlangen, Department of Medicine 3 – Rheumatology and Immunology, Erlangen, Germany*, *[3]Rheumatologist, Private Practice, Naunhof, Germany*, *[4]Rheumatologist, Private Practice, Goslar, Germany*, *[5]Charité Universitätsmedizin Berlin, , Berlin, Germany*

Background:

Based on results of the post-authorisation safety trial Oral Surveillance (OS, see [1]), the European and US-American regulatory agencies in 2021 issued warnings about malignancy risk associated with the Janus kinase inhibitor (JAKi) tofacitinib and required changes in labelling.

Objectives:

To analyse incident malignancies under treatment with JAKi, tumor necrosis factor inhibitors (TNFi), abatacept (ABA), rituximab (RTX), interleukin 6 inhibitors (IL6i) or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs - bionaive) in patients with rheumatoid arthritis (RA) observed in daily rheumatological care.

Methods:

Data from patients without cancer history from the biologics register RABBIT were included with treatment episodes started 01/2017 - 04/2022. Incidence rates (IR) of malignancies (without non melanoma skin cancer, NMSC) per 1000 patient-years (PY) with 95% confidence intervals (CI) and adjusted hazard ratios (HR) were calculated for all and selected patients according to OS inclusion criteria (age ≥ 50 years and ≥ 1 cardiovascular (CV) risk factor) to compare treatment groups to TNFi. Andersen-Gill regression analysis was used with a 6-month risk window, adjusted via stabilized and winsorized inverse probability of treatment weights taking into account age, sex, smoking, disease activity, prior therapies, comorbidities, and type of enrolling institution (clinic vs. private practice) as covariates. Multiple imputation of missing data was applied.

Results:

2763 JAKi, 3403 TNFi, 744 ABA, 834 RTX, 1125 IL6i and 1130 csDMARD initiations were documented. Patients with a JAKi start were less often men and (except RTX patients) slightly older and had a longer RA disease duration (table). The seropositive proportion and the number of prior treatments with biological (b) or targeted (ts) synthetic DMARDs was higher than in TNFi and csDMARD groups, but lower than in ABA and RTX groups.

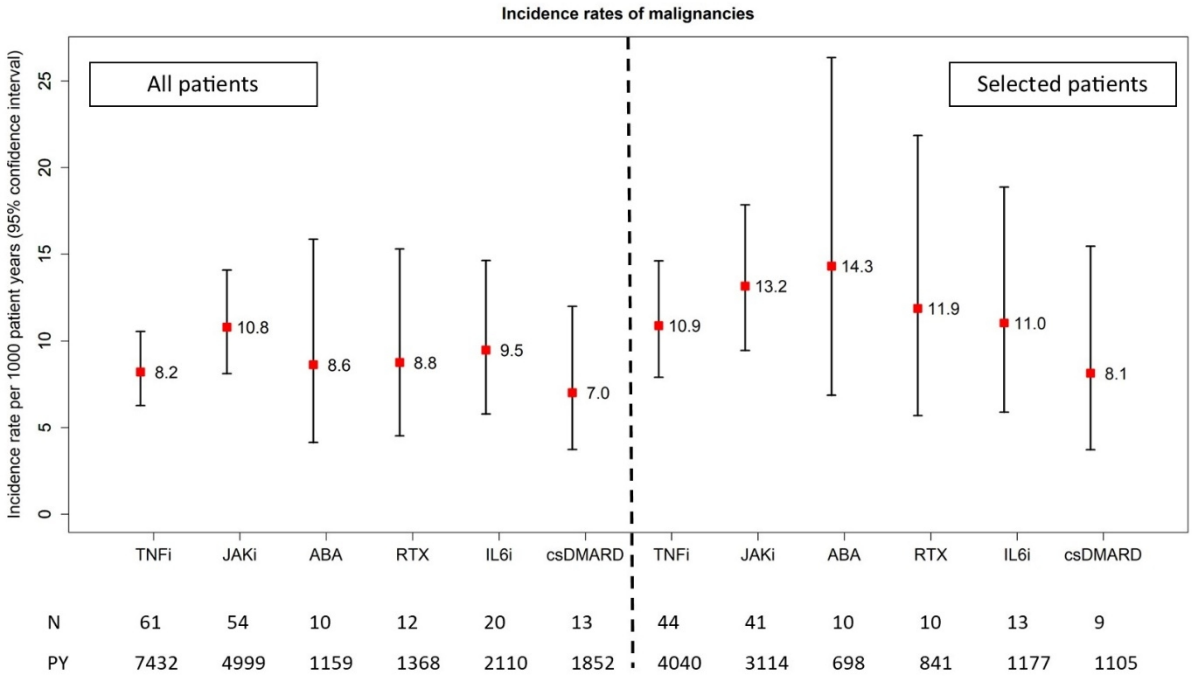
Table: Patient characteristics at the start of a DMARD episode.

ALL PATIENTS	**JAKi** n=2763	**TNFi** n=3403	**ABA** n=744	**RTX** n=834	**IL6i** n=1125	**csDMARD** n=1130
Age	59.9	57.3	59.6	61.5	58.6	59.6
Men	24%	26%	25.	30%	25%	27%
Disease duration	12.5	9.4	12.0	15.6	11.1	5.9
Seropositivity	79%	74%	81%	92%	79%	67%
# previous b/tsDMARDs	2.7	1.0	2.7	5.1	2.5	0
DAS28-ESR	4.2	4.3	4.4	3.7	4.3	4.2
% of full physical function	65.2	69.3	63.0	64.4	65.5	72.8
# comorbidities	2.2	1.8	2.4	2.5	2.0	1.5
Current smokers	26%	26%	27%	22%	26%	30%
SELECTED PATIENTS*	**JAKi** n=1665	**TNFi** n=1810	**ABA** n=444	**RTX** n=490	**IL6i** n=623	**csDMARD** n=645
Age	64.5	63.7	64.9	66.0	63.5	64.7
Men	27%	30%	29%	36%	28%	30%
Disease duration	13.5	10.2	13.1	16.0	11.9	6.4
Seropositivity	79%	73%	81%	90%	78%	67%
# previous b/tsDMARDs	2.8	1.0	2.7	5.2	2.5	0
DAS28-ESR	4.3	4.5	4.5	3.8	4.4	4.3
% of full physical function	61.5	64.7	59.5	61.7	61.2	70.3
# comorbidities	3.0	2.6	3.2	3.4	2.9	2.2
Current smokers	34%	37%	35%	28%	35%	38%

*Values are given as mean or percentage. *Age ≥50 years and ≥ 1 CV risk factor (hypertension, coronary heart disease, diabetes, hyperlipoproteinaemia, current smoking)*

151 incident malignancies were reported. Across treatments, patients showed comparable IRs between 7 and 11 events per 1000 PY. Among selected patients IRs were higher (13.2 events per 1000 PY in JAKi patients, 95% CI: 9.5 – 17.9). In adjusted analyses, neither JAKi (HR 1.06, 95% CI: 0.70 - 1.61), ABA (HR 0.73, 0.38 - 1.40), RTX (HR 0.86, 0.42 - 1.75), IL6i (HR 0.79, 0.45 - 1.40) nor csDMARDs (HR 2.07, 0.87 - 4.94) showed a significantly altered risk for malignancies compared with TNFi in unselected patients, with similar results in selected patients.

Figure: IRs of malignancies (without NMSC) per 1000 PY by treatment group



Conclusion:

IR of malignancies in selected patients receiving JAKi in a real-world setting was numerically higher than reported for tofacitinib in OS. However, we found no statistical evidence of an increased malignancy risk with JAKi compared to TNFi, although patients on JAKi were older and had longer disease duration and more previous b/tsDMARDs treatments. Further analyses assessing exposure in terms of treatment duration are needed.

References: [1] PMID: 35081280

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