Comparison of drug retention of TNF inhibitors, other biologics and JAK inhibitors in RA patients who discontinued JAK inhibitor therapy

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Abstract

Objectives: JAK Inhibitors (JAKi) are recommended DMARDs for patients with moderate-to severe rheumatoid arthritis (RA) who failed first-line therapy with methotrexate. There is a lack of data allowing an evidence-based choice of subsequent disease modifying anti-rheumatic drug (DMARD) therapy for patients who had discontinued JAKi treatment. We aimed to compare the effectiveness of TNF inhibitor (TNFi) therapy vs JAKi vs other mode of action (OMA) biologic DMARD (bDMARD) in RA patients who were previously treated with a JAKi.

Methods: RA patients who discontinued JAKi treatment within the Swiss RA registry SCQM were included for this observational prospective cohort study. Primary outcome was drug retention for either TNFi, OMA bDMARD or JAKi. The hazard ratio for treatment discontinuation was calculated adjusting for potential confounders. A descriptive analysis of the reasons for discontinuation was performed.

Results: 400 treatment courses of JAKi were included, with a subsequent switch to either JAKi, TNFi or OMA bDMARD. The crude overall drug retention was higher in patients switching to another JAKi as compared to TNFi and comparable to OMA. A significant difference of JAKi vs TNFi persisted after adjusting for potential confounders.

Conclusion: In a real-world population of RA patients who discontinued treatment with a JAKi, switching to another JAKi resulted in a higher drug retention than switching to a TNFi. A switch to a second JAKi seems an effective therapeutic option.

Key words: Rheumatoid arthritis, JAKi therapy, JAKi discontinuation, efficacy

Key messages:

- In a real-world population of RA patients who discontinued JAKi therapy, a switch to a second JAKi resulted in a higher drug retention as compared to switching to a TNFi.

Introduction

In recent years, a new class of small molecular DMARD targeting intracellular signaling molecules was approved for use in RA. These targeted synthetic DMARDs (tsDMARD) include inhibitors of Janus kinases (JAKi). In 2013 the first JAKi Tofacitinib was licensed in Switzerland for RA treatment, followed 2017 by Baricitinib and most recently Upadacitinib in 2020. In consideration of the comparable efficacy of JAK inhibitors with bDMARDs licensed for use in RA in randomised controlled trials, the revised EULAR recommendations of 2019 suggest TNFi and JAKi as an equal second line therapy for patients with moderate to severe RA refractory to methotrexate [1].

The efficacy of JAKi in patients with an inadequate response (IR) to methotrexate [2-4] as well as after TNF failure has been shown in phase III randomized clinical trials [5-8]. In contrast, there is a lack of data on the efficacy of TNFi, JAKi or biologics with other mode of action (OMA) in patients who have discontinued JAKi treatment.

In the SELECT-COMPARE study RA patients were randomized to treatment with either Upadacitinib or Adalimumab or placebo. In a treat-to-target study design the protocol allowed an immediate switch to the alternate active treatment as a rescue in case of non-response or incomplete response until week 26. The analysis of the patients who switched from Upadacitinib to Adalimumab or vice versa showed improvement in both switch groups with only 5% of patients who worsened at six months post switch, suggesting that TNFi therapy after previous JAKi is an effective therapeutic option. However, the study was not powered for a direct comparison of the two populations of patients [9].

The aim of our study was to compare the real-world effectiveness of treatment with TNFi or another JAKi or an OMA bDMARD in RA patients after the discontinuation of JAKi treatment.

Methods

Study Design and population

For this study we used data from the prospective longitudinal patient cohort of the Swiss clinical quality management (SCQM) for rheumatoid arthritis. The SCQM cohort has been described in detail previously [10]. Patients are enrolled by hospital-based rheumatologists as well as rheumatologists in private practice. Clinical data such as disease activity, laboratory parameters and patient reported outcomes are recorded regularly at follow up visits.

In accordance with the declaration of Helsinki all patients gave informed consent before inclusion in the SCQM cohort. This study has been approved by the respective ethics review board (EKNZ 2020-00018).

Study outcomes

The primary outcome of this study was the drug retention time after JAKi discontinuation (independent of reasons) as an indirect marker for treatment effectiveness and tolerance. Drug retention time can be regarded as a composite measure that accounts for both positive and negative therapeutic effects (e.g. adverse reactions, unacceptable costs and loss of efficacy) as well as for noise (non-compliance, psychological factors, misunderstanding)[11]. The time on treatment was defined as the period between the treatment start and the stop date (date of last dose) as recorded in the database.

We performed multivariable regression analysis to adjust for the following covariates: disease duration at baseline, sex, seropositivity (defined as RF or anti-CCP positivity), baseline HAQ, concomitant csDMARD therapy (yes or no), concomitant glucocorticoid therapy (yes or no), bDMARD history (naïve, 1, 2, >3), previous type of bDMARD (TNFi, OMA or JAKi) and reason for JAKi discontinuation to calculate the hazard ratios of treatment discontinuation for comparing the groups of interest.

Reasons for discontinuation of the JAKi therapy were recorded in the database as either: “not effective”, “adverse events”, “remission” or “other”. Free text entries in the database with detailed information on adverse events were available for analysis.

Inclusion Criteria and study period

Patients with a confirmed diagnosis of RA included in SCQM who discontinued, for any reason, treatment with one of the available JAKi: Tofacitinib, Baricitinib or Upadacitinib. The study period start was set to the Tofacitinib licensing date in Switzerland in August 2013 and all data captured until the end of 2020 were used for analysis.

Exposure of interest

The exposure of interest in our analysis was type of b/ts DMARD initiated after discontinuation of the previous JAKi. The following DMARD therapies were considered for analysis. TNFi, including Adalimumab, Etanercept, Certolizumab pegol, Golimumab or Infliximab; OMA bDMARD, including Abatacept, Sarilumab, Tocilizumab or Rituximab, and JAKi, including Tofacitinib, Baricitinib or Upadacitinib. Concomitant conventional synthetic (cs) DMARD therapy included Methotrexate, Sulfasalazine, Leflunomide, Azathioprine and Hydroxychloroquine.

Statistical Analysis

Baseline characteristics of the three different treatment groups (TNFi, OMA or alternative JAKi) after JAKi discontinuation were compared. P-values for the differences were derived by Kruskal-Wallis and Fisher’s exact test for continuous and categorical variables respectively. Treatment retention was summarized by Kaplan-Meier curves and the differences between the groups were evaluated by the log-rank test. Adjusted treatment retention analysis was performed by using Cox regression and adjusting for potential confounders at baseline. The validity of the model was

assessed by using appropriate diagnostic tools (log-minus-log survival plot, Schoenfeld residuals). The adjusted retention analysis was performed for both imputed and complete-case datasets. For the imputation we used multiple missing value imputation by chained equations (MICE) for the missing baseline covariates of HAQ score, seropositivity and disease duration. Missingness varied from 2% (disease duration, seropositivity) to 69% (HAQ score). A missing-at-random (MAR) data pattern was assumed. Along with HAQ score, seropositivity, disease duration, sex, age, bDMARD/csDMARD use and history, age, smoking, joint assessment, BMI, patient- and physician global assessment have been included in the imputation model as covariates. The MICE algorithm was run for 65 imputations and 25 iterations. Diagnostic measures were used to evaluate the convergence of the MICE algorithm and validity of imputed data.

Results

Effectiveness of TNFi vs OMA vs JAKi in patients who discontinued JAKi

In the SCQM RA database and during the study period, 364 patients amounting to a total of 400 treatment courses (TC) of JAKi (83.2% Tofacitinib (333 TC), 16.5% Baricitinib (66 TC) and 0.2% Upadacitinib (1 TC)) were observed. They were switched to either a therapy with TNFi (125 TC), OMA (194 TC) or another JAKi (81 TC). The duration of the JAKi therapy before the switch was in the mean 398 days and median 232 days. The reason for discontinuation of the JAKi indicated by the treating rheumatologist was ”not effective” in 57.2% (n = 229 TC), “adverse events” in 27.8% (n = 111 TCs) and “other” in 15 %.

Of the patients discontinuing JAKi treatment many had a treatment history with at least two different prior TNFi therapies (TNFi 37.6%, OMA 40.2%, JAKi 39.5%) or at least two OMA bDMARD (TNFi 36.0%, OMA 25.3%, JAKi 44.5%), TNFi naïve patients were less frequent in the OMA and JAKi groups (18.6% and 27.2%) compared to TNFi treated patients (33.6%) (Table 1). In the TNFi, OMA and JAKi

groups 26 (20.8%), 31 (16%) and 3 (3%) of the patients had been treated previously with the same drug. Further differences in the baseline characteristics included co-therapy and seropositivity. In between the three switch groups there were fewer patients with additional csDMARD co-therapy in the group switched to another JAKi compared to the OMA and the TNFi group (25.9% compared to 47.9% and 52.0%, p=0.0005). Also, fewer patients in the JAKi switch group were treated with concomitant steroid therapy (23.5% in the JAKi group, compared to 40.2% with OMA and 35.2% with TNFi, p=0.03). In the TNFi switch group the percentage of seropositivity (63.2%), was lower than in the group switched to OMA or JAKi (78.2%, 71.6%, p=0.01).

The median retention times were 335 days for the TNFi switch group, 508 days for OMA and 918 days for the JAKi switch group (Figure 1). The crude overall drug retention rate differed between the three groups, with the highest drug retention rate in patients switching to another JAKi, followed by OMA and TNFi (log-rank test p=0.0033).

Multivariable analysis adjusting for potential cofounders, revealed that the hazard ratio for drug discontinuation was lower in patients who switched to another JAKi (HR: 0.48, 95%CI 0.3 to 0.76) compared to those who switched to a TNFi (Table 2). The hazard ratio in patients who switched to OMA was also lower compared to TNFi (HR: 0.82, 95% CI 0.6 to 1.12)) but with no significant difference. However, this effect was lost when patients with Rituximab were excluded from the analysis (HR OMA vs TNF: 1.0, 95% CI 0.73 to1.36). Results from complete-case and imputed-data analysis were consistent in direction, effect size, and significance and leading to no difference in our results.

Reasons for discontinuation of JAKi before initiating TNFi, OMA or JAKi

The most frequently indicated reason for discontinuation was “not effective” (62,5% of stop reasons in TNFi, 50.5% in OMA and 40% in JAKi), followed by “adverse event” (23.6% of stop reasons in TNFi, 23.7% in OMA and 32.0% in JAKi).
We had detailed written information for 66.1% – 72.2% of the cases for which adverse events were indicated as the reason for discontinuation of JAK inhibitor before switching to either TNFi, OMA or JAKi (Table 3A). Regarding adverse events of special interest malignancy, major cardiac adverse events (MACE) and thromboembolism, one case of monoclonal gammopathy and 2 of pulmonary embolism were recorded. Infectious adverse events included 5 patients with Herpes simplex or Herpes zoster infections, that were exclusively switched to OMA bDMARD. For other side effects such as skin, gastrointestinal, other infections as well as nonspecific symptoms a balanced distribution between the treatment groups was found.
For the discontinuation reason “other”, diverse reasons were reported by the treating rheumatologists, including pregnancy, medication interactions, patient preference and nonspecific symptoms. Also, possible adverse events were reported, two malignancies, one cervical carcinoma and one melanoma and an ophthalmic herpes zoster all in the OMA bDMARD switch group (Table 3B).

Reasons of discontinuation for TNFi, OMA or JAKi in patients after discontinuation of JAKi

During our observation time of drug retention in patients who discontinued JAKi and switched to TNFi, OMA or another JAKi, we had 72 treatment stops of 125 TCs in TNFi, 97 of 194 TCs in OMA and 25 of 81 TCs in JAKi. The most frequent stop reason was ”not effective” (62.5% TNFi, 50.5 % OMA and 40% JAKi). For the stop reason “adverse events” we had detailed information in 64.7 – 100% with a wide variety of different reasons. Regarding adverse events of special interest there were

no reports on malignancy and thromboembolism, however the numbers at risk were low (Table 4).

Comparison of effectiveness of Tofacitinib vs Baricitinib in patients who discontinued TNFi treatment

Considering the fact that most of the patients analyzed in the group that discontinued JAKi treatment have switched from Tofacitinib to Baricitinib due to the later licensing of Baricitinib (Table 1), a potentially higher effectiveness of Baricitinib within the JAKi group might be a possible reason for the better drug retention of JAKi in patients who discontinued JAKi treatment in our analysis.

A subset analysis comparing drug retention of TNFi and OMA in patients with previous Tofacitinib versus previous Baricitinib treatment did not show a significant difference, however no adjusted analysis was possible due to the low number of patients with previous Baricitinib treatment (data not shown). We have therefore compared the effectiveness of Tofacitinib and Baricitinib in a larger group of patients in the SCQM cohort, that had discontinued a previous TNFi therapy (Baseline characteristics are shown in Supplementary Table S1, available at *Rheumatology* online).

The multivariate analysis showed no significant difference in the drug retention for Tofacitinib (reference) and Baricitinib in the imputed dataset (HR 0.73 (0.49 -1.09)) and the complete case analysis (HR 0.65 (0.32-1.29) (Supplementary Table S2, available at *Rheumatology* online). Similar results were obtained when a calendar restriction was applied and only patients included for analysis that started either Tofacitinib or Baricitinib after the licensing of Baricitinib on September 26, 2017 (data not shown).

Discussion

Recently, it was reported that patients with a primary insufficient response to the JAKi Upadacitinib demonstrated good responses after switching therapy to Adalimumab, with only 5% of patients experiencing a disease flare within 6 months after the rescue [9].

Our data from a real-world cohort of RA patients confirm these findings in a general manner for switching from JAKi to TNFi, and, importantly, add a comparison of effectiveness of JAKi, TNFi and OMA bDMARD in patients who discontinued JAKi treatment. We found a longer median drug retention time for patients who switched from one JAKi to another JAKi as compared to a TNFi, despite a higher percentage of concomitant csDMARDs and concomitant steroid intake in the TNFi population. These differences persisted after adjusting for potential confounders. OMA bDMARD compared to TNFi showed a non-significant trend for a longer median drug retention time. However, this effect was lost when patients treated with Rituximab were excluded. The discrepancy may be explained by the difficulty to clearly define discontinuation of Rituximab due to its long-term treatment effects with dosing intervals of six and more months.

In our cohort 39.3% of the patients (n=157) had a history of at least two prior TNFi treatments. The effectiveness of treatments is expected to decrease with the number of previous bDMARDs [12]. For patients who have failed TNFi treatment there is evidence that switching therapy to another mode of action DMARD is superior than switching to an alternative TNFi, at least after failure of two TNF inhibitors [13-15]. Decreasing effectiveness of treatment with Tofacinitib was seen in patients who have failed three or more bDMARDs [5], however this was not seen in a study with Baricitinib in patients that have failed two or more bDMARDs [16]. Whether treatment response declines with an increasing number of prior tsDMARD therapies is unknown. Therefore, to account for differences in previous TNFi and OMA bDMARD treatments we have adjusted for the bDMARD history and type of bDMARD in our analysis.

Due to historical reasons most of the patients were treated with Tofacitinib, which has been licensed in Switzerland already in 2013, and subsequently switched to Baricitinib. A recent clinical practice study suggested a higher effectiveness for Baricitinib as compared to Tofacitinib [17]. However, a metanalysis reported no difference between Tofacitinib and Baricitinib for ACR20, 50 and 70 responses [18]. At present time there are no published randomized trials directly comparing Tofacitinib and Baricitinib. Therefore, we cannot exclude the possibility, that the higher drug retention for JAKi in our study may have resulted because of a better effectiveness of Baricitinib as compared to Tofacitinib. Although a direct comparison of the two drugs in the population that discontinued JAKi treatment was not possible due to the low numbers of Baricitinib treated patients, we have compared the drug retention of Tofacitinib and Baricitinib in a larger population of patients in the SCQM cohort who discontinued a TNFi. We found no significant difference, suggesting that the better retention of JAKi was not solely due to differential effectiveness of the individual JAKi. In support of this conclusion, a recently published study on the comparative effectiveness of Tofacitinib and TNFi in the SCQM cohort showed a higher drug maintenance of Tofacitinib as compared to TNFi [19].

Recently, an increased risk for major cardiac adverse events (MACE) and malignancy was shown in a randomized safety study in patients with RA and cardiovascular risk factors treated with Tofacitinib [20]. The occurrence of cardiovascular events or cases of malignancies under JAKi treatment might influence choice of subsequent therapy. Our analysis of the reasons for discontinuation of the JAKi treatment showed no differences between the groups, arguing against a selection bias based on overall adverse events during the previous JAKi treatment. The detailed analysis of the free text entries in the database of the patients with stop reasons “adverse events” or “other” showed few cases of side effects of special interest. Two cases of malignancies and one case of monoclonal gammopathy were all switched to OMA bDMARD. Two cases of pulmonary embolism were reported,

both were switched to OMA bDMARD. Concerning infections there was overall a balanced distribution in the switch groups, with the exception of Herpes zoster and Herpes simplex infections, these patients were all switched to OMA bDMARD. This data suggests that in the case of adverse events of special interest OMA bDMARD seem to be the preferred choice.

There are limitations of our study. As therapy decisions in our real-world patient registry are at the discretion of the treating rheumatologists there may be an indication bias. Missingness of data is another limitation of registry studies. To account for missing baseline covariates in our data we have performed the analysis for both the subset of non-missing baseline information observations and the MICE imputed complete set of observations with similar and consistent results for the comparison of JAKi, TNFi or OMA after discontinuation of JAKi.

Since JAK inhibitors have been licensed for the treatment of RA recently, the patient numbers in our cohort were too small for sub-analyses, as well as for the analysis of possible predictors for therapeutic response and evaluation of the effectiveness of therapy in consideration of the stop reason of the previous JAKi treatment.
The strengths of our study are the real-world setting with a diversity of the patient population and the different treatments used in patients who discontinued JAKi therapy, as there are no restrictions in the use of bDMARD and JAKi in these patients in the Swiss health insurance system.
The results of our study indicate that switching to another JAKi is an effective therapeutic option in patients who discontinued JAKi and may be preferable over TNFi in patients who failed several previous bDMARD treatments. Randomized studies to confirm our findings and providing comparative safety data are needed.

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Ethics: All patients included in the SCQM registry have given written informed consent. The data was obtained in pseudonymized from the SCQM database. This study was approved by the responsible ethics review board (EKNZ 2020-00018)

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Author contributions: DK, MS and AS conceived the study. AA, DK and EP analysed the data. AA and DK wrote the manuscript. All authors reviewed the data and gave critical input.

Data availability statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1: Baseline characteristics for patients who discontinued JAKi and switched to TNFi, OMA or JAKi

Treatment group switched to (n)	TNFi (n=125) Adalimumab (22) Etanercept (30) Golimumab (31) Certolizumab (24) Infliximab (18)	OMA (n=194) Tocilizumab (71) Sarilumab (11) Abatacept (64) Rituximab (48)	JAKi (n=81) Baricitinib (73) Tofacitinib (4) Upadacitinib (4)	P value
Sex female n (%)	99 (79.2)	155 (79.9)	66 (81.5)	0.91
Age n (%)				0.15
<40 years	14 (11.2)	16 (8.2)	9 (11.1)	
40-60 years	66 (52.8)	95 (49.0)	30 (37.0)	
>60 years	45 (36.0)	83 (42.8)	40 (51.9)	
Disease duration (years), median (IQR)	12 (5-18) (n=123)	13 (5-18) (n=188)	15 (7 – 20) (n=81)	0.06
Seropositivity n (%)	79 (63.2)	151 (78.2)	58 (71.6)	0.02
Current Smoking n (%)	18 (26.5)	20 (19.8)	6 (13.3)	0.23
BMI (kg/m2), mean (SE)	25.9 (6.2) n=65	27.4 (5.8) n=103	26.2 (5.8) n=35	0.26
DAS28-CRP at baseline, mean (SE)	3.8 (1.4) n=63	4.0 (1.2) n=87	3.7 (1.1) n=39	0.57
HAQ at baseline, median (IQR)	1.0 (0.3-1.6) n=40	1.1 (0.7-1.6) n=54	0.9 (0.6-1.3) n=27	0.40
CDAI at baseline, median (IQR)	20.5 (11.0 – 24.0) n=25	24.9 (14.2 – 34.8) n=38	16.8 (11.0 -21.0) n=19	0.17
csDMARD	65 (52.0)	93 (47.9)	21 (25.9)	0.0005
Co-medication n (%)				
Previous JAKI n (%)				0.06
- **Tofacitinib**	102 (81.6)	158 (81.4)	73 (90.1)	
- **Baricitinib**	23 (18.4)	36 (18.6)	7 (8.6)	
- **Upadacitinib**			1 (1.2)	
Concomitant Steroids n (%)	44 (35.2)	78 (40.2)	19 (23.5)	0.03
Stop Reason JAKi n (%)				0.07
- **adverse event**	36 (28.8)	62 (32.0)	13 (16.1)	
- **not effective**	72 (57.6)	106 (54.6)	51 (63.0)	
- **remission**	0	0	0	
- **other reason**	17 (13.6)	26 (13.4)	17 (21.0)	
TNFi history n (%)				0.04
- Naive	42 (33.6)	36 (18.6)	22 (27.2)	
- 1	36 (28.8)	80 (41.2)	27 (33.3)	
- 2	21 (16.8)	47 (24.2)	18 (22.2)	
- ≥3	26 (20.8)	31 (16.0)	14 (17.3)	
OMA history n (%)				0.01
- Naive	48 (38.4)	82 (42.3)	26 (32.1)	
- 1	32 (25.6)	63 (32.5)	19 (23.5)	
- 2	23 (18.4)	31 (16.0)	14 (17.3)	
- ≥3	22 (17.6)	18 (9.3)	22 (27.2)	
JAKi history n (%)				0.97
- Naive	0	0	0	
- 1	112 (89.6)	169 (87.1)	71 (87.7)	
- 2	12 (9.6)	23 (11.9)	9 (11.1)	

- ≥3	1 (0.8)	2 (1.0)	1 (1.2)

OMA = biologics with other mode of action, IQR = interquartile range, SE = standard error, n = numbers of treatment courses, seropositivity = Anti citrullinate peptide and/or rheumatoid factor
When missing baseline covariates existed, we provide the total number (n) of treatment courses with available data per variable.

Table 2: Adjusted analysis of drug retention in patients who discontinued JAKi and switched to TNFi, OMA or JAKi

Switched to	HR (mice)	HR (cc)
TNFi	reference	reference
OMA	0.82(0.6, 1.12)	0.76 (0.44, 1.34)
JAKi	0.48 (0.3, 0.76)	0.42 (0.19, 0.91)

Adjusted retention analysis and Hazard ratios (HR) for the comparisons of interest for complete case (cc) and mice imputed data (mice).

Table 3A: Reported stop reason "adverse events" for discontinuation of JAKi before initiating TNF/OMA or JAKi

Treatment group switched to	TNFi	OMA	JAKi
Detailed reported adverse events n (%)*	26 (72.2)	41 (66.1)	9 (69.2)
Malignancy		Monoclonal gammopathy (1)	
Skin	Drug eruption (1) Acne (1)	Rash (2) Rosacea (1) Hematoma (1)	Pruritus (1)
Venous thromboembolism		Pulmonary embolism (2)	
Infection	Pneumonia (2) Urinary tract infection (1)	Recurrent Infections (2) Herpes simplex pharyngitis (1) Recurrent herpes simplex (3) Aseptic meningitis (1) Herpes zoster (1) Sepsis with Neisseria meningitis (1)	Recurrent Infections (3) Pulmonary actinomycosis (1)
Hematologic		Anemia (2)	
Gastrointestinal	Diarrhea (3) Liver enzymes elevation (1)	Diarrhea (1) Liver enzymes elevation (3)	Liver enzymes elevation (1)
Not effective		2	1
nonspecific symptoms	Dizziness (1) Flatulence (1) Headaches (4) Malaise (2) Hair loss (1) Cough (1)	Sleep disorder (2) Myalgia (1) Headaches (4) Malaise (1) Cough (1) Palpitations (1)	Dyspepsia (1) Weight gain (2)

	Dyspnea (2) Myalgia (1) Fear of side effects (1) Nausea (1) Weight gain (1)	Dysgeusia (1) Weight gain (2)
Various	Aphtous ulcers (2)	Hypertension (2) Blue toe syndrom (1)

** Percentage of total adverse events as stop reason for JAKi before switching to TNFi/OMA or another JAKi. n = number of events*

Table 3B: Reported stop reasons „other" for discontinuation of JAKi before initiating TNF/OMA or JAKi

Treatment group switched to	**TNFi**	**OMA**	**JAKi**
Written reported stop reasons "other" n (%)*	8 (47.1)	14 (53.8)	11 (64.7)
Malignancy (n)		Cervical carcinoma (1) Melanoma (1)	
Skin (n)		Rash (1)	Pruritus (1) Acne (1) Dermatitis/Rosacea (1)
Infection (n)	Erysipela (1)	Ophtalmic herpes zoster (1)	Pulmonary infection (1)
Hematologic (n)		Anemia (1)	Anemia (1)
Medication Interaction (n)			Voluconazole (1)
Surgery (n)		Elective stoma surgergy (1)	
Planned pregnancy (n)	2	1	
Not effective (n)		1	1
Remission (n)		1	2
Various (n)	Malaise (2) Anxiety (1) Dysphagia/Odynophagia (1) Weight gain (1)	Malcompliance (2) Fear of thrombosis (1) Hair loss (1) Weight gain (1)	Emigration (1) Weight gain (1)

** Percentage of total reported stop reasons "other", n = number of events*

Table 4: Stop reasons for patients treated with TNFi/OMA/JAKi after JAKi discontinuation

Treatment group switched to	**TNFi**	**OMA**	**JAKi**	**P value**
Stop reasons n (%)				0.36
- adverse events	17 (23.6)	23 (23.7)	8 (32.0)	
- not effective	45 (62.5)	49 (50.5)	10 (40.0)	
- remission	1 (1.4)	4 (4.1)	1 (4.0)	

- other reason	9 (12.5)	21 (21.6)	6 (24.0)
Detailed reported adverse events (n) % *	11 (64.7)	20 (87.0)	8/8 (100)
- Skin	Injection site reaction (1) Pruritus (2) Lipoma (1) Psoriasis (1) Allergic reaction (1)	Injection site reaction (1) Pruritus (1) Rash (1) Allergic rash (1)	Pruritus (1)
- Infection	Joint infection (1)	Otitis media (1) Recurrent herpes simplex (1) Neutropenia/Septic Shock (1)	Recurrent infections (1) Aseptic meningitis (1)
- Hematologic			Anemia (1)
- Gastrointestinal	Vomitus (1)	Elevated Transaminases (2) Vomitus (1)	Elevated Transaminases (1)
- Pulmonary	Dyspnea (1) Asthma exacerbation (1)	Asthma exacerbation (1)	
- Various	Aggravation of sarcoidosis (1)	High cholesterol (1) IgG4 related disease (1) Hypertension (3) Polyarthralgia (1) Asthenia (1) Myalgia (1) Aphtous ulcers (1)	Rhabdomyolysis (1) Fear of side effects (1) Weight gain(1)
** percentage of total stop reasons adverse events, n= number of events*			

Figure legends

Figure 1: Drug retention after JAKi discontinuation and switch to either TNFi, OMA or another JAKi. Median retention times for the 400 treatment courses are for TNFα-inhibitor (TNFi) 335, for other mode of action biologics (OMA) 508 and for JAK inhibitor (JAKi) 918 days. The x-axis is restricted to 600 days as most treatment discontinuations are observed up to that point. Numbers at risk are shown for TNFi (in red), OMA (in blue) and JAKi (in green). The p-value corresponds to the log-rank test.

Abbreviations

bDMARD	biological disease-modifying antirheumatic drug
CDAI	Clinical disease activity index
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DAS-28-CRP	Disease Activity Score 28
HAQ	Health Assessment Questionnaire
HR	Hazard Ratio
IQR	Interquartile Range
JAKi	Janus Kinase Inhibitor
MACE	Major adverse cardiac event
OMA	biological DMARD with other mode of action
RA	Rheumatoid Arthritis
SCQM	Swiss clinical quality management in rheumatic diseases registry
SE	standard error of the mean
TC	treatment courses
TNFi	Tumor necrosis factor inhibitor

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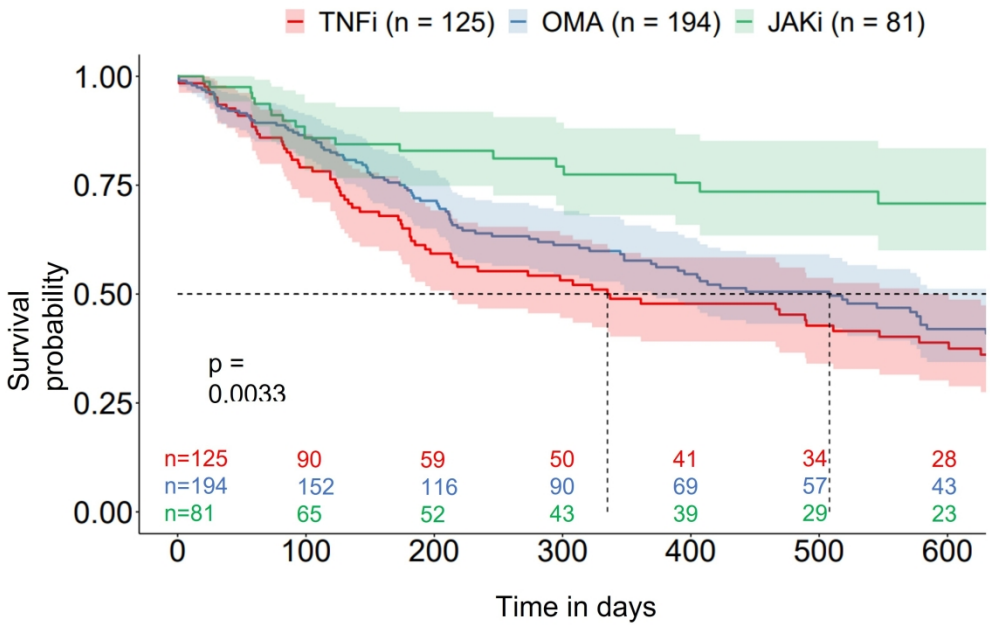

Figure 1. Drug retention after JAKi discontinuation and switch to either TNFi, OMA or another JAKi

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