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

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3 **Comparison of drug retention of TNF inhibitors, other biologics and JAK**
4 **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.

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3 Reasons for discontinuation of the JAKi therapy were recorded in the database as
4 either: “not effective”, “adverse events”, “remission” or “other”. Free text entries in the
5 database with detailed information on adverse events were available for analysis.
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10 11 Inclusion Criteria and study period

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

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

46 Baseline characteristics of the three different treatment groups (TNFi, OMA or
47 alternative JAKi) after JAKi discontinuation were compared. P-values for the
48 differences were derived by Kruskal-Wallis and Fisher’s exact test for continuous and
49 categorical variables respectively. Treatment retention was summarized by Kaplan-
50 Meier curves and the differences between the groups were evaluated by the log-rank
51 test. Adjusted treatment retention analysis was performed by using Cox regression
52 and adjusting for potential confounders at baseline. The validity of the model was
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3 assessed by using appropriate diagnostic tools (log-minus-log survival plot,
4 Schoenfeld residuals). The adjusted retention analysis was performed for both
5 imputed and complete-case datasets. For the imputation we used multiple missing
6 value imputation by chained equations (MICE) for the missing baseline covariates of
7 HAQ score, seropositivity and disease duration. Missingness varied from 2%
8 (disease duration, seropositivity) to 69% (HAQ score). A missing-at-random (MAR)
9 data pattern was assumed. Along with HAQ score, seropositivity, disease duration,
10 sex, age, bDMARD/csDMARD use and history, age, smoking, joint assessment, BMI,
11 patient- and physician global assessment have been included in the imputation
12 model as covariates. The MICE algorithm was run for 65 imputations and 25
13 iterations. Diagnostic measures were used to evaluate the convergence of the MICE
14 algorithm and validity of imputed data.
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30 **Results**

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

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33 In the SCQM RA database and during the study period, 364 patients amounting to a
34 total of 400 treatment courses (TC) of JAKi (83.2% Tofacitinib (333 TC), 16.5%
35 Baricitinib (66 TC) and 0.2% Upadacitinib (1 TC)) were observed. They were
36 switched to either a therapy with TNFi (125 TC), OMA (194 TC) or another JAKi (81
37 TC). The duration of the JAKi therapy before the switch was in the mean 398 days
38 and median 232 days. The reason for discontinuation of the JAKi indicated by the
39 treating rheumatologist was "not effective" in 57.2% (n = 229 TC), "adverse events" in
40 27.8% (n = 111 TCs) and "other" in 15 %.

41
42 Of the patients discontinuing JAKi treatment many had a treatment history with at
43 least two different prior TNFi therapies (TNFi 37.6%, OMA 40.2%, JAKi 39.5%) or at
44 least two OMA bDMARD (TNFi 36.0%, OMA 25.3%, JAKi 44.5%), TNFi naïve
45 patients were less frequent in the OMA and JAKi groups (18.6% and 27.2%)
46 compared to TNFi treated patients (33.6%) (Table 1). In the TNFi, OMA and JAKi
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3 groups 26 (20.8%), 31 (16%) and 3 (3%) of the patients had been treated previously
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5 with the same drug. Further differences in the baseline characteristics included co-
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7 therapy and seropositivity. In between the three switch groups there were fewer
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9 patients with additional csDMARD co-therapy in the group switched to another JAKi
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11 compared to the OMA and the TNFi group (25.9% compared to 47.9% and 52.0%,
12
13 $p=0.0005$). Also, fewer patients in the JAKi switch group were treated with
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15 concomitant steroid therapy (23.5% in the JAKi group, compared to 40.2% with OMA
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17 and 35.2% with TNFi, $p=0.03$). In the TNFi switch group the percentage of
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19 seropositivity (63.2%), was lower than in the group switched to OMA or JAKi (78.2%,
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21 71.6%, $p=0.01$).

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24 The median retention times were 335 days for the TNFi switch group, 508 days for
25
26 OMA and 918 days for the JAKi switch group (Figure 1). The crude overall drug
27
28 retention rate differed between the three groups, with the highest drug retention rate
29
30 in patients switching to another JAKi, followed by OMA and TNFi (log-rank test
31
32 $p=0.0033$).

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35 Multivariable analysis adjusting for potential cofounders, revealed that the hazard
36
37 ratio for drug discontinuation was lower in patients who switched to another JAKi
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39 (HR: 0.48, 95%CI 0.3 to 0.76) compared to those who switched to a TNFi (Table 2).
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41 The hazard ratio in patients who switched to OMA was also lower compared to TNFi
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43 (HR: 0.82, 95% CI 0.6 to 1.12) but with no significant difference. However, this effect
44
45 was lost when patients with Rituximab were excluded from the analysis (HR OMA vs
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47 TNF: 1.0, 95% CI 0.73 to 1.36). Results from complete-case and imputed-data
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49 analysis were consistent in direction, effect size, and significance and leading to no
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51 difference in our results.

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56 *Reasons for discontinuation of JAKi before initiating TNFi, OMA or JAKi*
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3 The most frequently indicated reason for discontinuation was “not effective” (62,5%
4 of stop reasons in TNFi, 50.5% in OMA and 40% in JAKi), followed by “adverse
5 event” (23.6% of stop reasons in TNFi, 23.7% in OMA and 32.0% in JAKi).
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9 We had detailed written information for 66.1% – 72.2% of the cases for which
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11 adverse events were indicated as the reason for discontinuation of JAK inhibitor
12
13 before switching to either TNFi, OMA or JAKi (Table 3A). Regarding adverse events
14
15 of special interest malignancy, major cardiac adverse events (MACE) and
16
17 thromboembolism, one case of monoclonal gammopathy and 2 of pulmonary
18
19 embolism were recorded. Infectious adverse events included 5 patients with Herpes
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21 simplex or Herpes zoster infections, that were exclusively switched to OMA
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23 bDMARD. For other side effects such as skin, gastrointestinal, other infections as
24
25 well as nonspecific symptoms a balanced distribution between the treatment groups
26
27 was found.
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31 For the discontinuation reason “other”, diverse reasons were reported by the treating
32
33 rheumatologists, including pregnancy, medication interactions, patient preference
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35 and nonspecific symptoms. Also, possible adverse events were reported, two
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37 malignancies, one cervical carcinoma and one melanoma and an ophthalmic herpes
38
39 zoster all in the OMA bDMARD switch group (Table 3B).
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42 43 *Reasons of discontinuation for TNFi, OMA or JAKi in patients after discontinuation of* 44 45 *JAKi*

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47 During our observation time of drug retention in patients who discontinued JAKi and
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49 switched to TNFi, OMA or another JAKi, we had 72 treatment stops of 125 TCs in
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51 TNFi, 97 of 194 TCs in OMA and 25 of 81 TCs in JAKi. The most frequent stop
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53 reason was “not effective” (62.5% TNFi, 50.5 % OMA and 40% JAKi). For the stop
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55 reason “adverse events” we had detailed information in 64.7 – 100% with a wide
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57 variety of different reasons. Regarding adverse events of special interest there were
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3 no reports on malignancy and thromboembolism, however the numbers at risk were
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5 low (Table 4).
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10 *Comparison of effectiveness of Tofacitinib vs Baricitinib in patients who discontinued*
11 *TNFi treatment*
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14 Considering the fact that most of the patients analyzed in the group that discontinued
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16 JAKi treatment have switched from Tofacitinib to Baricitinib due to the later licensing
17
18 of Baricitinib (Table 1), a potentially higher effectiveness of Baricitinib within the JAKi
19
20 group might be a possible reason for the better drug retention of JAKi in patients who
21
22 discontinued JAKi treatment in our analysis.
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25 A subset analysis comparing drug retention of TNFi and OMA in patients with
26
27 previous Tofacitinib versus previous Baricitinib treatment did not show a significant
28
29 difference, however no adjusted analysis was possible due to the low number of
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31 patients with previous Baricitinib treatment (data not shown). We have therefore
32
33 compared the effectiveness of Tofacitinib and Baricitinib in a larger group of patients
34
35 in the SCQM cohort, that had discontinued a previous TNFi therapy (Baseline
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37 characteristics are shown in Supplementary Table S1, available at *Rheumatology*
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39 online).
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42 The multivariate analysis showed no significant difference in the drug retention for
43
44 Tofacitinib (reference) and Baricitinib in the imputed dataset (HR 0.73 (0.49 -1.09))
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46 and the complete case analysis (HR 0.65 (0.32-1.29) (Supplementary Table S2,
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48 available at *Rheumatology* online). Similar results were obtained when a calendar
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50 restriction was applied and only patients included for analysis that started either
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52 Tofacitinib or Baricitinib after the licensing of Baricitinib on September 26, 2017 (data
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54 not shown).
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58 **Discussion**
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3 Recently, it was reported that patients with a primary insufficient response to the
4 JAKi Upadacitinib demonstrated good responses after switching therapy to
5 Adalimumab, with only 5% of patients experiencing a disease flare within 6 months
6 after the rescue [9].
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11 Our data from a real-world cohort of RA patients confirm these findings in a general
12 manner for switching from JAKi to TNFi, and, importantly, add a comparison of
13 effectiveness of JAKi, TNFi and OMA bDMARD in patients who discontinued JAKi
14 treatment. We found a longer median drug retention time for patients who switched
15 from one JAKi to another JAKi as compared to a TNFi, despite a higher percentage
16 of concomitant csDMARDs and concomitant steroid intake in the TNFi population.
17
18 These differences persisted after adjusting for potential confounders. OMA bDMARD
19 compared to TNFi showed a non-significant trend for a longer median drug retention
20 time. However, this effect was lost when patients treated with Rituximab were
21 excluded. The discrepancy may be explained by the difficulty to clearly define
22 discontinuation of Rituximab due to its long-term treatment effects with dosing
23 intervals of six and more months.
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26
27 In our cohort 39.3% of the patients (n=157) had a history of at least two prior TNFi
28 treatments. The effectiveness of treatments is expected to decrease with the number
29 of previous bDMARDs [12]. For patients who have failed TNFi treatment there is
30 evidence that switching therapy to another mode of action DMARD is superior than
31 switching to an alternative TNFi, at least after failure of two TNF inhibitors [13-15].
32
33 Decreasing effectiveness of treatment with Tofacitinib was seen in patients who have
34 failed three or more bDMARDs [5], however this was not seen in a study with
35 Baricitinib in patients that have failed two or more bDMARDs [16]. Whether treatment
36 response declines with an increasing number of prior tsDMARD therapies is
37 unknown. Therefore, to account for differences in previous TNFi and OMA bDMARD
38 treatments we have adjusted for the bDMARD history and type of bDMARD in our
39 analysis.
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3 Due to historical reasons most of the patients were treated with Tofacitinib, which
4 has been licensed in Switzerland already in 2013, and subsequently switched to
5 Baricitinib. A recent clinical practice study suggested a higher effectiveness for
6 Baricitinib as compared to Tofacitinib [17]. However, a metanalysis reported no
7 difference between Tofacitinib and Baricitinib for ACR20, 50 and 70 responses [18].
8
9 At present time there are no published randomized trials directly comparing
10 Tofacitinib and Baricitinib. Therefore, we cannot exclude the possibility, that the
11 higher drug retention for JAKi in our study may have resulted because of a better
12 effectiveness of Baricitinib as compared to Tofacitinib. Although a direct comparison
13 of the two drugs in the population that discontinued JAKi treatment was not possible
14 due to the low numbers of Baricitinib treated patients, we have compared the drug
15 retention of Tofacitinib and Baricitinib in a larger population of patients in the SCQM
16 cohort who discontinued a TNFi. We found no significant difference, suggesting that
17 the better retention of JAKi was not solely due to differential effectiveness of the
18 individual JAKi. In support of this conclusion, a recently published study on the
19 comparative effectiveness of Tofacitinib and TNFi in the SCQM cohort showed a
20 higher drug maintenance of Tofacitinib as compared to TNFi [19].
21
22 Recently, an increased risk for major cardiac adverse events (MACE) and
23 malignancy was shown in a randomized safety study in patients with RA and
24 cardiovascular risk factors treated with Tofacitinib [20]. The occurrence of
25 cardiovascular events or cases of malignancies under JAKi treatment might influence
26 choice of subsequent therapy. Our analysis of the reasons for discontinuation of the
27 JAKi treatment showed no differences between the groups, arguing against a
28 selection bias based on overall adverse events during the previous JAKi treatment.
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30 The detailed analysis of the free text entries in the database of the patients with stop
31 reasons “adverse events” or “other” showed few cases of side effects of special
32 interest. Two cases of malignancies and one case of monoclonal gammopathy were
33 all switched to OMA bDMARD. Two cases of pulmonary embolism were reported,
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3 both were switched to OMA bDMARD. Concerning infections there was overall a
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5 balanced distribution in the switch groups, with the exception of Herpes zoster and
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7 Herpes simplex infections, these patients were all switched to OMA bDMARD. This
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9 data suggests that in the case of adverse events of special interest OMA bDMARD
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11 seem to be the preferred choice.
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16 There are limitations of our study. As therapy decisions in our real-world patient
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18 registry are at the discretion of the treating rheumatologists there may be an
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20 indication bias. Missingness of data is another limitation of registry studies. To
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22 account for missing baseline covariates in our data we have performed the analysis
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24 for both the subset of non-missing baseline information observations and the MICE
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26 imputed complete set of observations with similar and consistent results for the
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28 comparison of JAKi, TNFi or OMA after discontinuation of JAKi.
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33 Since JAK inhibitors have been licensed for the treatment of RA recently, the patient
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35 numbers in our cohort were too small for sub-analyses, as well as for the analysis of
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37 possible predictors for therapeutic response and evaluation of the effectiveness of
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39 therapy in consideration of the stop reason of the previous JAKi treatment.
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42 The strengths of our study are the real-world setting with a diversity of the patient
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44 population and the different treatments used in patients who discontinued JAKi
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46 therapy, as there are no restrictions in the use of bDMARD and JAKi in these
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48 patients in the Swiss health insurance system.
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51 The results of our study indicate that switching to another JAKi is an effective
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53 therapeutic option in patients who discontinued JAKi and may be preferable over
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55 TNFi in patients who failed several previous bDMARD treatments. Randomized
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57 studies to confirm our findings and providing comparative safety data are needed.
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Acknowledgements:

We would like to thank all patients and rheumatologists for contributing data to the SCQM. A list of rheumatology offices and hospitals that are contributing to the SCQM registries can be found on www.scqm.ch/institutions. The SCQM is financially supported by pharmaceutical companies. A list of current sponsors can be found on www.scqm.ch/sponsors.

Funding: This SCQM work has been performed with financial contribution from AbbVie.

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)

Disclosures: DK has received personal fees from AbbVie, Gilead, Janssen, Eli-Lilly, Novartis and Pfizer. AF has received personal fees from AbbVie, Eli-Lilly, Galapagos, Mylan, MSD, Pfizer and Sanofi. PV received speaker honorary, advisory fees and/or research support from Roche, MSD, Abbvie, Pfizer, Novartis, Grünenthal, Amgen, Sanofi, Chugai, BMS, Gilead. BM has received personal fees from Abbvie, Amgen, Celgene, Novartis, Pfizer. ARR received honoraria for lectures and consultation from Abbvie, Pfizer, Lilly, Gilead, Janssen, Novartis, UCB, Amgen. MS is an employee of AbbVie AG.

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.

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3 **Data availability statement:** All data relevant to the study are included in the article
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5 or uploaded as supplementary information.
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Table 1: Baseline characteristics for patients who discontinued JAKi and switched to TNFi, OMA or JAKi

Treatment group switched to (n)	TNFi (n=125)	OMA (n=194)	JAKi (n=81)	P value
	Adalimumab (22) Etanercept (30) Golimumab (31) Certolizumab (24) Infliximab (18)	Tocilizumab (71) Sarilumab (11) Abatacept (64) Rituximab (48)	Baricitinib (73) Tofacitinib (4) Upadacitinib (4)	
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)
<p>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.</p>			

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 nonspecific symptoms	Dizziness (1) Flatulence (1) Headaches (4) Malaise (2) Hair loss (1) Cough (1)	2 Sleep disorder (2) Myalgia (1) Headaches (4) Malaise (1) Cough (1) Palpitations (1)	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	Aphthous 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)	Ophthalmic herpes zoster (1)	Pulmonary infection (1)
Hematologic (n)		Anemia (1)	Anemia (1)
Medication Interaction (n)			Voluconazole (1)
Surgery (n)		Elective stoma surgery (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) Aphthous ulcers (1)	Rhabdomyolysis (1) Fear of side effects (1) Weight gain(1)
<i>* percentage of total stop reasons adverse events, n= number of events</i>			

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 TNF α -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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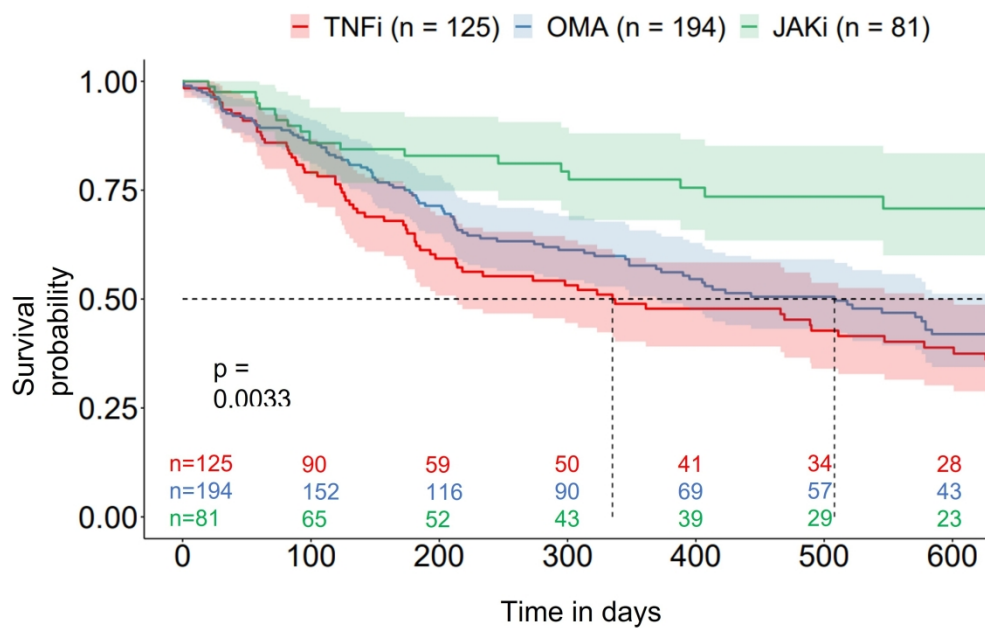


Figure 1. Drug retention after JAKi discontinuation and switch to either TNFi, OMA or another JAKi

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