# Real-world utilisation and switching between Janus kinase inhibitors in Australian patients with rheumatoid arthritis in the OPAL Dataset

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## Abstract

### Objective

*To describe use and treatment persistence for Janus kinase inhibitors (JAKi) in rheumatoid arthritis (RA) by line of therapy, and the mechanism of action for the drug switched to after JAKi discontinuation.*

### Methods

*This was a retrospective, observational analysis using the OPAL dataset, a large collection of deidentified electronic medical records from 112 rheumatologists around Australia. Adult patients with RA were included if they initiated tofacitinib (TOF), baricitinib (BARI) or upadacitinib (UPA) between 1 October 2015 and 30 September 2021. Data were summarised using descriptive statistics. Kaplan-Meier survival was used to analyse treatment persistence.*

### Results

*5,900 patients initiated JAKi within the study window (TOF n=3,662, BARI n=1,875, UPA n=1,814). Median persistence was similar across JAKi within each line of therapy where there was sufficient follow-up, and almost 3 years for first-line: 34.9 months (95% CI 30.8, 40.7; n=1,408) for TOF, 33.6 months (95% CI 25.7, not reached; n=545) for BARI. While JAKi to JAKi switching occurred across all lines of therapy, switches to a tumour necrosis factor inhibitor (TNFi) were more frequent after first- or second-line JAKi. JAKi monotherapy use at baseline increased with line of therapy, and was highest at follow-up after switching to another JAKi. 'Lack of efficacy' was the most common reason for discontinuing JAKi.*

### Conclusion

*In this large analysis of Australian real-world practice separated by line of therapy, treatment persistence for JAKi was high overall subject to differential follow-up, but declined in later lines. JAKi to JAKi switching was observed across all lines of therapy.*

**Key words**

rheumatoid arthritis, JAK inhibitor, b/tsDMARD, treatment switching

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## Introduction

Janus kinase inhibitors (JAKi) have been a major development for the treatment of rheumatoid arthritis (RA) due to their ability to block multiple cytokine pathways involved in disease pathogenesis (1). Several of these molecules have become available for RA globally and in Australia, three different JAKi are available for RA: tofacitinib (TOF), baricitinib (BARI) and upadacitinib (UPA), available since October 2015, September 2018 and May 2020, respectively. These drugs target different receptor-associated tyrosine kinases of the JAK family, resulting in different cytokine modulation profiles (2). There is now a growing interest in understanding how different JAKi are being used in the real-world setting.

A deeper understanding of the underlying pathogenesis of RA, coupled with the personalised tailoring of treatment decisions according to patient characteristics, represents crucial focal points in the advancement of RA management (3, 4). There are multiple studies supporting switching for patients with RA who have not responded to tumour necrosis factor inhibitor (TNFi), either to another TNFi or an agent with a different mechanism of action (MOA) (5, 6). At present there are limited data on the choice of next agent for patients who discontinue JAKi. At present there are limited data to inform these choices. Recent real-world data, especially from the large JAK-pot study, on how JAKi have been used and outcomes after discontinuation and switching from JAKi have been important for understanding how JAKi contribute to treatment options for RA (7-12).

The Australian setting is useful for learning about the real-world use of different biologic or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD) classes because there are no restrictions on the order in which these classes can be prescribed. Once a patient with moderate to severe RA qualifies for government subsidisation of a b/tsDMARD, their rheumatologist can prescribe any approved b/tsDMARD according to clinical need. Patients can then be switched to another agent within the same or other class at the rheumatologist's discretion. In the context of this study, this means that in Australia JAKi can be prescribed as the first b/tsDMARD received by a patient as well as in later lines of therapy, and cycling between JAKi as well as switching to and from agents with other MOA can occur.

The Optimising Patient outcomes in Australian rheumatoLogy (OPAL) dataset is a collection of electronic medical records (EMR) from a large number of patients around Australia, including 54,900 patients with RA (13). The objectives of this study were to describe the uptake, use and persistence of JAKi in the OPAL dataset, separated by line of therapy, and to describe the therapeutic approaches taken when JAKi were discontinued.

## Methods

*Data source*

OPAL Rheumatology is a consortium of rheumatologists who all use a specific EMR called Audit4 (Software 4 Specialists, Pty Ltd), which has been customised for rheumatology (13). Deidentified clinical data captured at the point-of-care are extracted from all participating sites on a quarterly basis and aggregated to create the OPAL dataset (14). At present 112 rheumatologists (approximately one third of Australian rheumatologists) practising in 43 predominantly private community-based clinics around Australia are contributing their clinical records to this initiative. Patients consent to the use of their deidentified data for research via an opt-out consent model. In accordance with the Declaration of Helsinki, the University of New South Wales Human Research Ethics Committee has approved the use of deidentified data captured during routine care in the OPAL dataset for research purposes (HC17799), and this specific protocol (HC210612).

Eligible patients with moderate to severe RA can access government subsidisation for any approved b/tsDMARD. The study window for this analysis was 1 October 2015 until 30 September 2021, to reflect the earliest dates when JAKi became available in Australia. However, it is important to note that the different JAKi have been available for

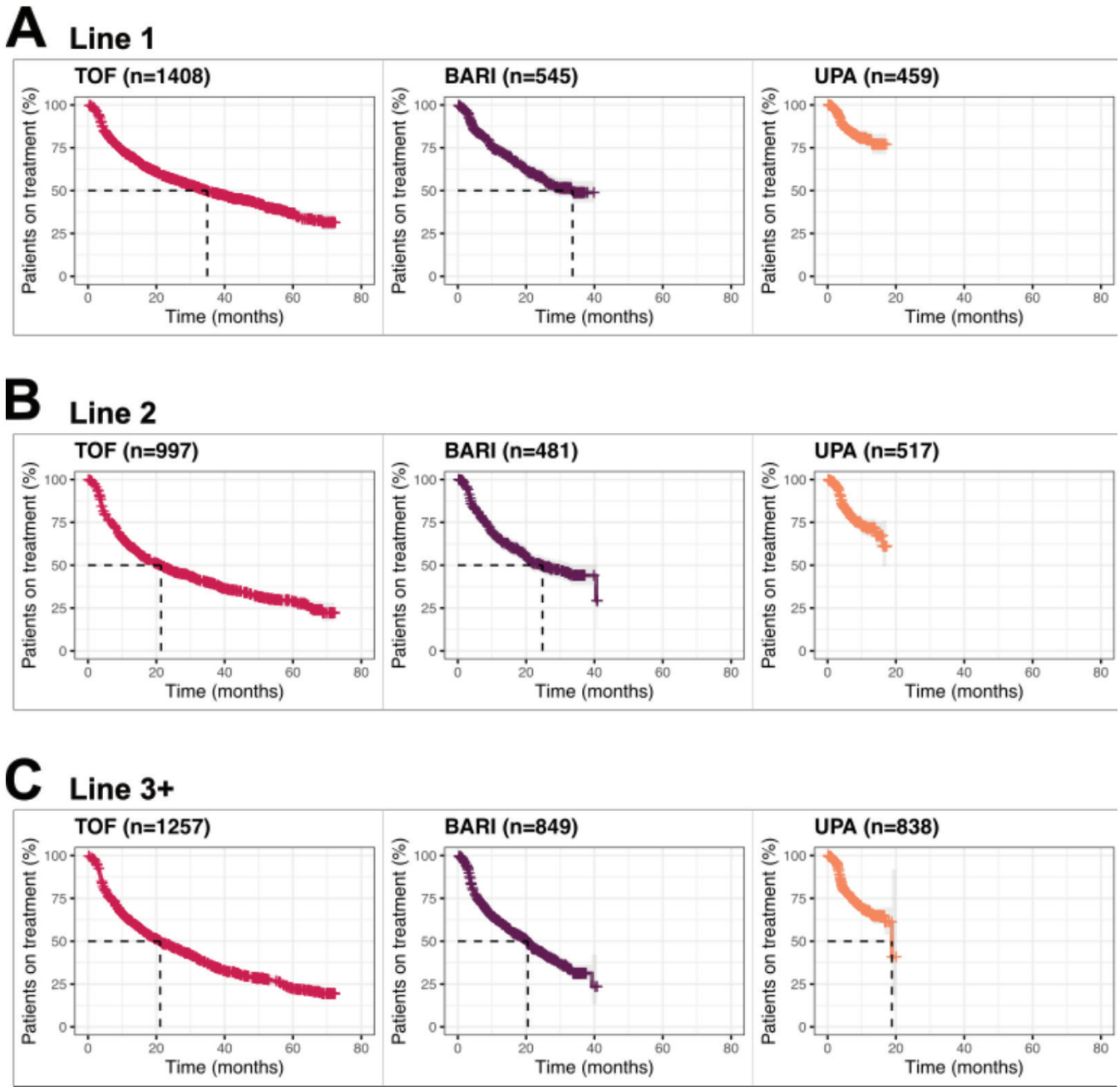


**Fig. 1.** Persistence on JAKi treatment for patients with RA who initiated BARI, TOF or UPA as (**A**) first-line, (**B**) second-line or (**C**) third-line or later. Dashed lines indicate median drug survival, *i.e.* time to 50% of patients stopping treatment. Maximum observation periods were 72 months for TOF, 37 months for BARI and 17 months for UPA.

different amounts of time in Australia: October 2015 for TOF, September 2018 for BARI and May 2020 for UPA. This limits the amount of possible follow-up time for the later drugs, especially for UPA, and has implications for the interpretation of this study. Our analysis did not adjust for these differences in available follow-up time. However, a sensitivity analysis was performed in which only treatment switches that occurred after 2020 were included.

Data extracted for this study included demographics, disease history, comorbidities, prescribed medications, and pathology and disease activity measures at baseline, switch and follow-up. These included swollen joint count-28 (SJC28), tender joint count-28 (TJC28), C-reactive protein (CRP), the patient global score and the Disease Activity Score-28 with CRP (DAS28CRP). As a requirement for government reimbursement, disease activity is assessed at baseline, then 3 months follow-up and 6-monthly intervals thereafter. Follow-up timepoints of 3 months and 9 months were used in this analysis for the description of b/tsDMARD monotherapy status at follow-up.

*Participants*

Adult patients diagnosed with RA (ICD10 M05 or M06) were eligible for inclusion in this study if they initiated a JAKi drug (TOF, BARI or UPA) within

**Table I.** Baseline characteristics for patients who initiated a JAKi as first-line, second-line or third-line or later.

| Feature[a] | Category | Line 1 | | | Line 2 | | | Line 3+ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TOF (n=1,408) | BARI (n=545) | UPA (n=459) | TOF (n=997) | BARI (n=481) | UPA (n=517) | TOF (n=1,257) | BARI (n=849) | UPA (n=838) |
| Age, years (median, IQR; range); 100%, 100%, 100% Gender (n, %); 98.8%, 98.9%, 99.4% | - | 61 [52–70]; 17–88 | 62 [51–70]; 18–89 | 60 [50.5–69]; 22–88 | 61 [52–69], 19–90 | 62 [52–70], 17–90 | 61 [51–70], 18–92 | 59 [50–68]; 19–89 | 60 [51–70]; 20–90 | 61 [53–69]; |
| | Female | 1035 (74.0%) | 391 (72.7%) | 315 (70.8%) | 748 (75.7%) | 366 (77.1%) | 390 (76.5%) | 1037 (82.8%) | 681 (80.8%) | 663 (80%) |
| | Male | 364 (26.0%) | 147 (27.3%) | 130 (29.2%) | 240 (24.3%) | 109 (22.9%) | 120 (23.5%) | 216 (17.2%) | 162 (19.2%) | 166 (20%) |
| Recorded disease duration, years (median, IQR; range); 100%, 100%, 100% | - | 1.1 [0.3–3.5]; 0–11.5 | 1.3 [0.5–4.4]; 0–12.4 | 1.8 [0.7–4.5]; 0–13.5 | 2.7 [1.3–5.7]; 0–11.7 | 3.3 [1.8–7.5]; 0–14.6 | 3.3 [1.8–7.5]; 0–14.6 | 5.2 [3–6.8]; 0–15.2 | 6.3 [3.4–9.1]; 0–14 | 7 [4.0–10.2]; 0–15.9 |
| JAKi initiated as monotherapy or in combination with a csDMARD (n, %); 100%, 100%, 100%[b] | Monotherapy | 337 (23.9%) | 118 (21.7%) | 116 (25.3%) | 387 (38.8%) | 209 (43.5%) | 259 (50.1%) | 530 (42.2%) | 386 (45.5%) | 530 (57.4%) |
| | Combination | 1,071 (76.1%) | 427 (78.3%) | 343 (74.7%) | 610 (61.2%) | 272 (56.5%) | 258 (49.9%) | 727 (57.8%) | 463 (54.5%) | 357 (42.6%) |
| | Combination including MTX[c] | 827 (77.2%) | 346 (81.0%) | 259 (75.5%) | 496 (81.3%) | 203 (74.6%) | 198 (76.7%) | 598 (82.3%) | 373 (80.6%) | 277 (77.6%) |
| Pre-existing comorbidities (n, %); 29.8%, 37.0%, 30.5%[d] | Renal disease | 19 (1.3%) | 6 (1.1%) | 9 (2.0%) | 27 (2.7%) | 11 (2.3%) | 14 (2.7%) | 17 (1.4%) | 17 (2.0%) | 22 (2.6%) |
| | Cardiac disease | 44 (3.1%) | 20 (3.7%) | 16 (3.5%) | 51 (5.1%) | 33 (6.9%) | 33 (6.4%) | 39 (3.1%) | 41 (4.8%) | 42 (5.0%) |
| | Hypertension | 207 (14.7%) | 77 (14.1%) | 67 (14.6%) | 217 (21.8%) | 123 (25.6%) | 151 (29.2%) | 200 (15.9%) | 152 (17.9%) | 182 (21.7%) |
| | Venous thrombo-embolism | 17 (1.2%) | 3 (0.6%) | 3 (0.7%) | 17 (1.7%) | 7 (1.5%) | 7 (1.4%) | 14 (1.1%) | 5 (0.6%) | 12 (1.4%) |
| | All cancer | 124 (8.8%) | 62 (11.4%) | 39 (8.5%) | 196 (19.7%) | 127 (26.4%) | 120 (23.2%) | 173 (13.8%) | 135 (15.9%) | 154 (18.4%) |
| | Historical shingles | 22 (1.6%) | 14 (2.6%) | 6 (1.3%) | 51 (5.1%) | 26 (5.4%) | 31 (6.0%) | 32 (2.5%) | 31 (3.7%) | 52 (6.2%) |
| DAS28CRP (median, IQR; range); 33.3%, 39.4%, 42.3%[e] | - | 5.3 [4.2–6.2]; 1.2–8.1 | 5.1 [4.4–6.1]; 1.2–8.3 | 5.6 [4.4–6.4; 1.2–7.9 | 3.4 [2.5–4.7]; 1.2–7.8 | 3.5 [2.3–4.6]; 1.2–7.5 | 3.2 [1.9–4.3]; 1.2–7.7 | 3.6 [2.7–4.8]; 1.3–8 | 3.6 [2.4–4.8]; 1.2–8 | 3 [2.1–4]; 1.1–7.6 |
| DAS28CRP (n, %); 33.3%, 39.4%, 42.3%[e] | Remission | 39 (9.2%) | 9 (5.0%) | 16 (8.1%) | 107 (27.9%) | 65 (31.2%) | 74 (37.9%) | 115 (22.2%) | 105 (27.2%) | 128 (37.5%) |
| | Low | 14 (3.3%) | 1 (0.6%) | 2 (1.0%) | 62 (16.2%) | 22 (10.6%) | 21 (10.8%) | 74 (14.3%) | 48 (12.4%) | 58 (17.0%) |
| | Moderate | 136 (31.9%) | 73 (40.8%) | 56 (28.4%) | 140 (36.6%) | 85 (40.9%) | 75 (38.5%) | 225 (43.4%) | 162 (42.0%) | 118 (34.6%) |
| | High | 237 (55.6%) | 96 (53.6%) | 123 (62.4%) | 74 (19.3%) | 36 (17.3%) | 25 (12.8%) | 104 (20.1%) | 71 (18.4%) | 37 (10.9%) |

[a]Percentages in this column indicate data completeness for first-line, second-line and third-line or later, respectively
[b]Combination therapy defined as methotrexate, hydroxychloroquine, leflunomide or sulfasalazine concomitantly prescribed at the time of first JAKi prescription
[c]Percentages of patients receiving a JAKi in combination with methotrexate (MTX) out of total patients receiving a JAKi in combination with any of methotrexate, hydroxychloroquine, leflunomide or sulfasalazine
[d]Percentage reflects the number of patients with any pre-existing complications recorded at baseline, which are likely to be under-recorded
[e]Percentages of missing DAS28CRP for each JAKi by line of therapy were: 30.3%, 32.8% and 42.9% for TOF, BARI and UPA, respectively, in line 1; 38.4%, 43.2% and 37.7% for TOF, BARI and UPA, respectively, in line 2; and 41.2%, 45.5% and 40.7% for TOF, BARI and UPA, respectively, in line 3+

the study window. Patients who had died or who were aged over 95 years were excluded in compliance with the overarching ethics for research using the OPAL dataset (HC17799). Patients were not excluded if they had missing data on any baseline characteristics.

*Data management and definitions*

To minimise the impact of missing outcomes data at baseline, if disease activity was not recorded at baseline, then the closest date on which disease activity was assessed within 1 month prior or 1.5 months after baseline was used instead. In practice, 87.5% of these dates on which disease activity was recorded were the baseline date, and 96.0% of them were within 2 weeks either side of baseline (Suppl. Fig. S1). While disease activity was reported at baseline in this manner, disease activity at follow-up was not described due to high proportions of missing data. Prescribed medications included conventional synthetic (cs)DMARDs (methotrexate, hydroxychloroquine, leflunomide or sulfasalazine) and b/tsDMARDs. In this analysis, monotherapy refers to b/tsDMARD monotherapy and combination therapy refers to a b/tsDMARD received in combination with at least one csDMARD.

Line of therapy was defined with reference to b/tsDMARD therapy, such that first-line means first-recorded b/tsDMARD and so on. This definition was not restricted to only the b/tsDMARDs received within the study window, and so b/tsDMARDs initiated prior to the study window still counted as lines of therapy. Consequently, a small proportion of the patients had a prior JAKi that was initiated before 1 October 2015, before their first JAKi initiated within the study window.

A treatment switch was defined as a b/tsDMARD initiated subsequent to an earlier b/tsDMARD regardless of any time

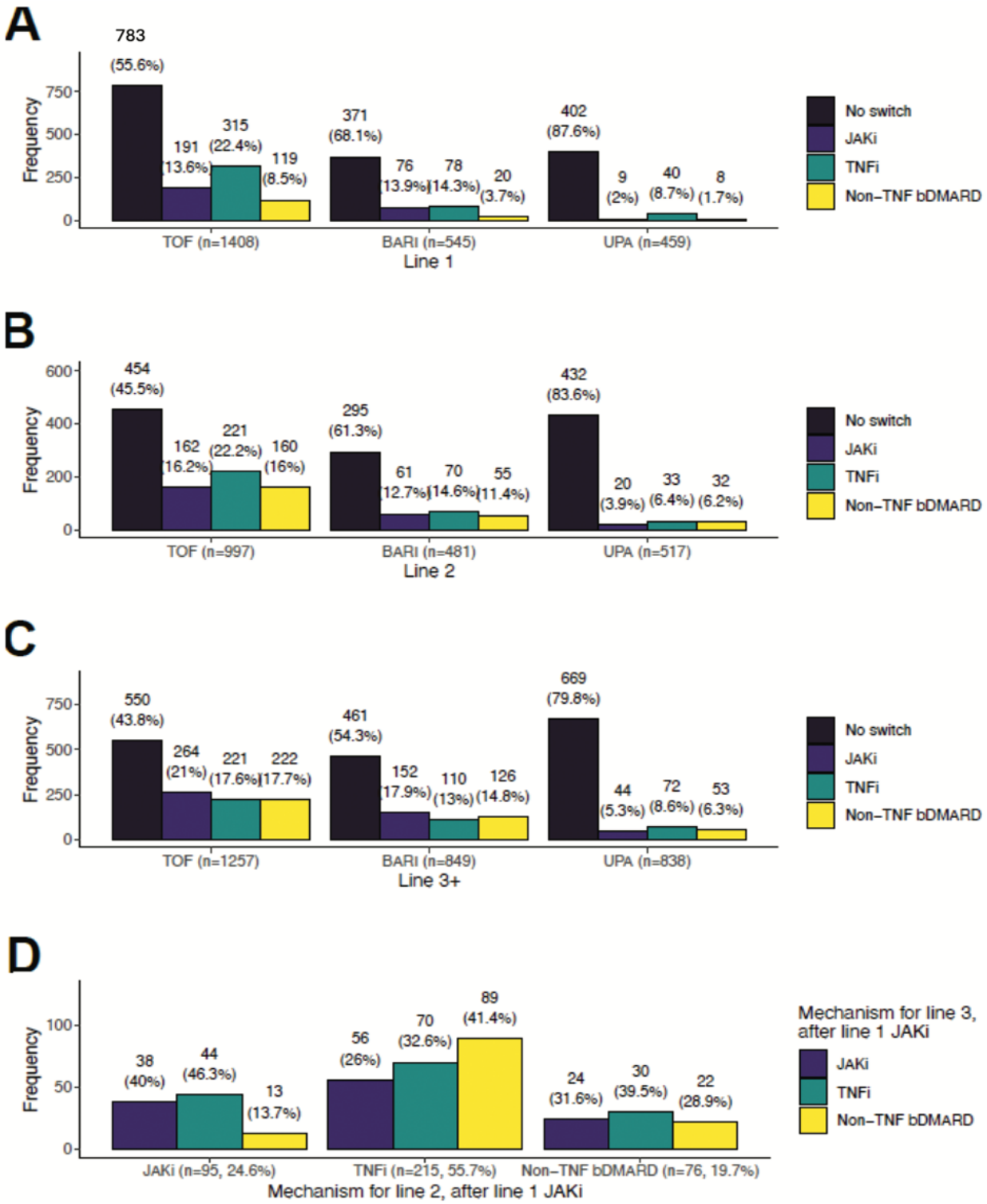


**Fig. 2.** MOA of b/tsDMARD switched to for patients who initiated a JAKi.
Switches from (**A**) first-line, (**B**) second-line or (**C**) third-line or later. (**D**) MOA for second-line and third-line b/tsDMARD switched to for 386 patients who initiated JAKi as first-line and had two subsequent switches (depicted across x-axis and using colour, respectively). Within each panel the frequency on the y axis refers to the absolute number of patients. Maximum observation periods were 72 months for TOF, 37 months for BARI and 17 months for UPA.

lag between these two b/tsDMARDs, as any switch was considered clinically relevant. In practice, almost 90% of subsequent b/tsDMARDs were initiated on the same date on which the prior b/tsDMARD was stopped. When the date on which a medication was initiated or ceased was not recorded by the rheumatologist, then automatic date-stamps generated by the Audit4 EMR software for every prescription were used to infer when b/tsDMARD and csDMARD were initiated or ceased. csDMARD stop dates were missing more frequently than b/tsDMARD start or stop dates.

**Table II.** Characteristics of patients at time of switch for patients who switched from JAKi at first-line, second-line, or third-line or later.

| Feature[a] | Category | Line 1 | | | Line 2 | | | Line 3+ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TOF (n=625) | BARI (n=174) | UPA (n=57) | TOF (n=543) | BARI (n=186) | UPA (n=85) | TOF (n=707) | BARI (n=388) | UPA (n=169) |
| JAKi as monotherapy or in combination therapy status at time of JAKi switch (n, %); 100%, 100%, 100%[b] | Monotherapy | 235 (37.6%) | 62 (35.6%) | 13 (22.8%) | 235 (43.3%) | 95 (51.1%) | 43 (50.6%) | 315 (44.6%) | 174 (44.8%) | 101 (59.8%) |
| | Combination | 390 (62.4%) | 112 (64.4%) | 44 (77.2%) | 308 (56.7%) | 91 (48.9%) | 42 (49.4%) | 392 (55.4%) | 214 (55.2%) | 68 (40.2%) |
| | Combination including MTX[c] | 316 (81.0%) | 88 (78.6%) | 34 (77.3%) | 257 (83.4%) | 78 (85.7%) | 37 (88.1%) | 342 (87.2%) | 194 (90.7%) | 54 (79.4%) |
| Reason for discontinuation JAKi (n, %); 68.8%, 77.1%, 82.0%[d] | Lack of efficacy | 139 (33.3%) | 53 (41.1%) | 16 (39.0%) | 154 (36.9%) | 58 (38.7%) | 22 (35.5%) | 197 (33.3%) | 107 (34.0%) | 39 (29.5%) |
| | Completed treatment/no longer required[e] | 101 (24.2%) | 35 (27.1%) | 8 (19.5%) | 90 (21.6%) | 27 (18.0%) | 11 (17.7%) | 144 (24.4%) | 68 (21.6%) | 44 (33.3%) |
| | Better alternative | 93 (22.2%) | 18 (14.0%) | 3 (7.3%) | 98 (23.5%) | 31 (20.7%) | 9 (14.5%) | 122 (20.6%) | 69 (22.0%) | 9 (6.8%) |
| | Adverse reaction | 64 (15.3%) | 18 (14.0%) | 12 (29.3%) | 52 (12.5%) | 30 (20.0%) | 16 (25.8%) | 84 (14.2%) | 56 (17.8%) | 38 (28.8%) |
| | Contraindication | 6 (1.4%) | 2 (1.6%) | 0 (0%) | 4 (1.0%) | 1 (0.7%) | 1 (1.6%) | 3 (0.5%) | 3 (1.0%) | 0 (0%) |
| | Patient non-adherence | 4 (1.0%) | 2 (1.6%) | 0 (0%) | 5 (1.2%) | 2 (1.3%) | 1 (1.6%) | 8 (1.4%) | 2 (0.6%) | 0 (0%) |
| | Other | 11 (2.6%) | 1 (0.8%) | 2 (4.9%) | 14 (3.4%) | 1 (0.7%) | 2 (0.3.2%) | 33 (5.6%) | 10 (3.2%) | 2 (1.5%) |

[a]Percentages in this column indicate data completeness for first-line, second-line and third-line or later, respectively
[b]Combination therapy defined as methotrexate, hydroxychloroquine, leflunomide or sulfasalazine concomitantly prescribed at the time of first JAKi prescription
[c]Percentages of patients receiving a JAKi in combination with methotrexate (MTX) out of total patients receiving a JAKi in combination with any of methotrexate, hydroxychloroquine, leflunomide or sulfasalazine
[d]Denominator for the percentages of each category is out of those that discontinued
[e]Not believed that 'Completed treatment/no longer required' means drug-free remission in this context.

*Statistical analysis*

All analyses were performed using R version 4.0.2 (15). Data were summarised using descriptive statistics: counts and percentages for categorical data, median, interquartile range (IQR) and full range for continuous data. Treatment persistence was analysed using non-parametric Kaplan-Meier survival analysis and the 'survival' package in R (16-18). Median survival (time to 50% of patients stopping treatment) and 25$^{th}$ centile (time to 25% of patients stopping treatment) are reported, along with 95% confidence intervals (CI). In this analysis of drug survival, patients were right-censored if they were lost to follow-up or if they had not experienced a treatment cessation event by the end of the study period and were recorded as currently on JAKi. Less than 10% of patients were lost to follow-up. Where estimates or upper 95% CI are reported as "not reached" (NR), this is because insufficient patients have stopped treatment for these to have been estimated and reflects the differing durations of follow-up time available for the three drugs.

As this was a descriptive analysis, formal statistical hypothesis testing was not performed and adjustments were not made for covariates in analysis of drug survival. Patients with missing data were not excluded in order to maintain a representative cohort and avoid selection bias. Percentages of complete data are reported for all variables.

## Results

*Uptake and persistence for JAKi across different lines of therapy*

Of the 54,900 patients with RA in the OPAL dataset, 12,211 were prescribed at least one b/tsDMARD within the study window (Suppl. Fig. S2). A large number of patients initiated at least one JAKi drug during this period (n=5,900). Notably, 2,412 patients initiated a JAKi as their first-line b/tsDMARD, including 1,408 initiations of TOF, 545 initiations of BARI and 459 initiations of UPA (Fig. 1). Of the 1,995 and 2,944 patients who initiated a JAKi as their second-line or third-line or later b/tsDMARD, 997 and 1,257 initiated TOF, 481 and 849 initiated BARI, and 517 and 838 initiated UPA, respectively. The maximum observation periods were 72 months for TOF, 37 months for BARI and 17 months for UPA, which are the consequences of the different dates when these agents were introduced to the Australian market. Patients who initiated JAKi had similar characteristics and disease activity scores at baseline within each line of therapy (Table I). The ICD10 codes used to define the pre-existing conditions as listed in Table I are given in Supplementary Table S1.

Within each line of therapy group, persistence on treatment was similar overall across the three JAKi where there was sufficient follow-up (Fig. 1, Suppl. Table S2). Patients who initiated JAKi as first-line had the most months of treatment persistence. Among patients who initiated a JAKi as first-line, median drug survival was 34.9 months (95% CI 30.8, 40.7; n=1,408) for TOF and 33.6 months (95% CI 25.7, NR; n=545) for BARI. When JAKi were used in second-line, persistence reduced to 21.4 months (95% CI 18.2, 24.8; n=997) for TOF and 24.8 months (95% CI 20.1, NR; n=481) for BARI. There were insufficient patients who initiated UPA as first-line or second-line and insufficient follow-up to estimate median survival. Median drug survival was also similar when JAKi was used as third-line or

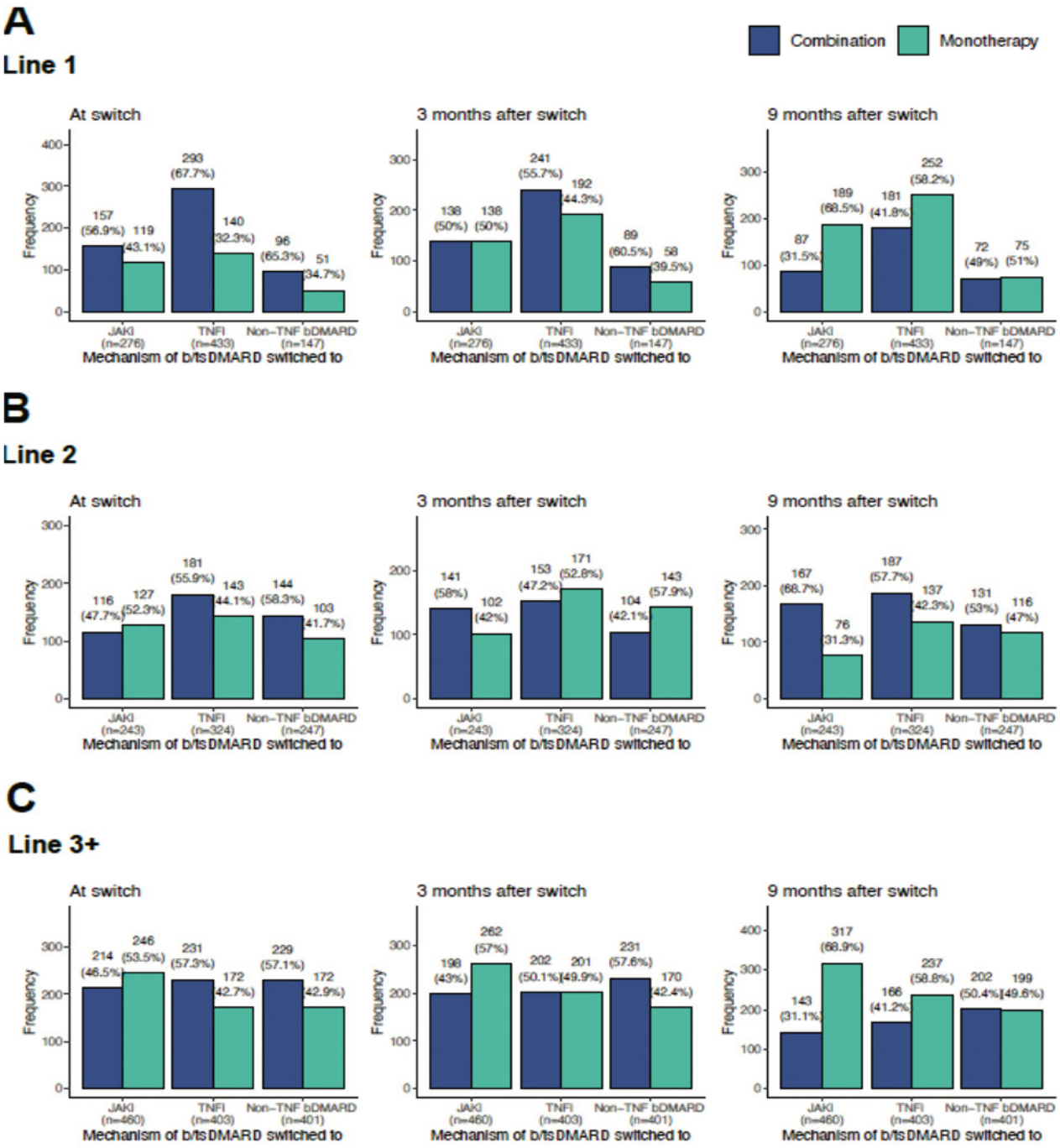


**Fig. 3.** JAKi monotherapy or JAKi/csDMARD combination therapy status for patients who switched from JAKi to another JAKi, TNFi or other bDMARD. Switches from JAKi initiated as (**A**) first-line, (**B**) second-line, and (**C**) third-line or later. Within each panel the frequency on the y axis refers to the absolute number of patients.

later: 21.1 months (95% CI 18.5, 24.4; n=1,257) for TOF, 20.5 months (95% CI 17.5, 21.8; n=849) for BARI, and 18.8 (95% CI 18.8, NR; n=838) for UPA.

*MOA of b/tsDMARDs switched to from JAKi*

The majority of patients who initiated a JAKi remained on this agent throughout the study window (Fig. 2). The different proportions of patients who did not switch and remained on treatment across the three JAKi are likely to reflect the different amounts of time these drugs have been available.

The rate of switching increased slightly with line of therapy, with 856 (35.5%) of first-line JAKi, 814 (40.8%) of second-line JAKi and 1,264 (42.9%) of third-line or later JAKi switching to a subsequent b/tsDMARD (Fig. 2). Higher proportions of patients who switched from first-line or second-line JAKi were switched to a TNFi. For example, 45–70% of patients were switched from first-line JAKi to a TNFi and around 40% were switched from second-line JAKi to a TNFi, while around 16–-44% and 24–33% of switches from first-line and second-line JAKi, respectively,

were to another JAKi (Fig. 2A-2B). By contrast, JAKi to JAKi switching at later lines of therapy was more frequent, with approximately 40% of switches being to another JAKi (Fig. 2C). Non-TNFi bDMARDs were more frequently used in later lines of therapy. When analysis was restricted to treatment switches that occurred after 2020 when UPA became available, there were higher proportions of switching from TOF and BARI to JAKi rather than TNFi (Suppl. Table S3).

Treatment switches were also described for patients who switched from first-line JAKi to two subsequent b/tsDMARDs. For example, there were 386 patients who switched from a first-line JAKi to a second- and third-line b/tsDMARD. Of these patients who had first- and second-line JAKi, interestingly 38 (40.0%) switched to a third JAKi and 44 (46.3%) switched to a TNFi (Fig. 2D).

Over 60% of patients who switched from first-line JAKi were receiving JAKi in combination with at least one csDMARD at the time of switch. The proportion of patients who were on b/tsDMARD monotherapy at the time of switch was higher for patients who switched from JAKi at later lines of therapy (Table II). For patients who were receiving a csDMARD in combination with JAKi, most of these csDMARDs were methotrexate. The proportion of patients on b/tsDMARD monotherapy consistently increased at the 3- and 9-month follow-up timepoints after switch, irrespective of the MOA of the subsequent b/tsDMARD (Fig. 3). Interestingly, when patients switched from one JAKi to another JAKi, a higher proportion were on monotherapy at follow-up across all lines of therapy. For example, 43.1% of patients who switched from first-line JAKi to another JAKi were on monotherapy at switch and many patients discontinued csDMARDs afterwards (50.0% and 68.5% at 3 and 9 months after switch) (Fig. 3A).

The reason for discontinuing treatment was documented by the rheumatologist in the patient's EMR at the time of the decision from a pre-defined menu. Lack of efficacy' was the most frequently recorded reason for switching from JAKi

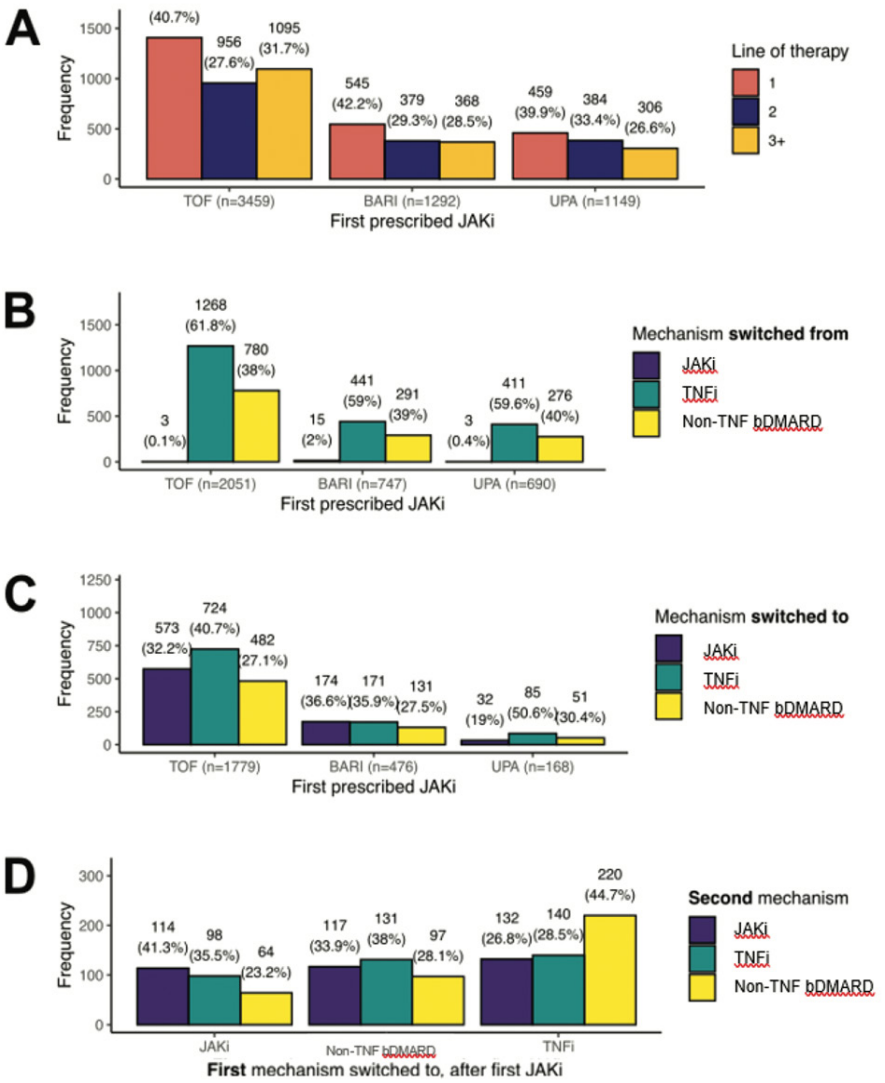


**Fig. 4.** Switching patterns for patients who initiated their first JAKi.
**A**: Line of therapy for first prescribed JAKi.
**B**: MOA of b/tsDMARD switched from, to first prescribed JAKi. A small proportion of patients initiated another JAKi prior to the beginning of the study window.
**C**: MOA of b/tsDMARD switched to, from first prescribed JAKi.
**D**: MOA of first and second agents switched to, after first prescribed JAKi (depicted across x-axis and using colour, respectively). Within each panel the frequency on the y axis refers to the absolute number of patients.

across all lines of therapy (Table II). A small proportion of patients initiating a JAKi experienced an adverse reaction prompting treatment cessation.

*Switching patterns after first-prescribed JAKi*

Among the 5,900 patients with RA who initiated JAKi, the first JAKi that patients were prescribed was frequently also their first-line b/tsDMARD (Fig. 4A). For patients who switched from another bDMARD to their first JAKi, approximately 60% of these switches were from a TNFi (Fig. 4B). Similar to the findings for switches from first-line JAKi, a large proportion of switches from first-prescribed JAKi were to a TNFi, but there were also high levels of switching to another JAKi from patients' first JAKi (Fig. 4C).

Of the patients who initiated a JAKi, 1,113 patients had two subsequent b/tsDMARDs after their first JAKi. Within these patients, 276 (24.8%) received a second JAKi and of these, 114 (41.3%) went on to a third JAKi drug, indicating JAKi to JAKi to JAKi switching (Fig. 4D). For patients who were switched to a TNFi after their first JAKi and re-

ceived a subsequent b/tsDMARD, the highest proportion of these switches was to a non-TNFi bDMARD (n=220, 44.7%).

## Discussion

Our analysis of the OPAL dataset shows that there has been high uptake of JAKi for RA in the Australian setting, including as first-line b/tsDMARD, and the baseline characteristics of patients initiating JAKi are similar. The strength of this study is the large number of patients (5,900) who initiated a JAKi within a single country and regulatory setting. Large numbers enabled all analyses to be separated by line of therapy. Although follow-up time was not equivalent, treatment persistence was broadly similar across TOF, BARI and UPA within each line of therapy. Among patients who ceased JAKi, there were many who switched to another JAKi across all lines of therapy, and especially at later lines. Interestingly, this included a group of patients who cycled only between three different JAKi. Lack of efficacy was the most frequent reason for ceasing JAKi.

Most patients who switched from a JAKi had received JAKi in combination with a csDMARD at the time of switching, but the proportion of patients no longer requiring concomitant csDMARDs increased at follow-up. Additionally, higher proportions of patients who switched from JAKi to another JAKi were on monotherapy at switch, and higher proportions of patients who switched to another JAKi ceased concomitant csDMARDs at follow-up. However, there are multiple possible explanations for the cessation of csDMARDs after switching. These include better disease control but also side effects from the csDMARD, patient preference or clinician perception of efficacy of JAKi when used as monotherapy.

This study supports the results from other real-world studies of JAKi, most notably the European multi-country JAK-pot collaboration, which showed treatment retention was similar for JAKi and other bDMARD classes compared to TNFi in an analysis that included 7,686 JAKi treatment courses (7). A subsequent analysis from the JAK-pot dataset, which included 365 patients who switched from JAKi to JAKi and 1,635 patients who switched from JAKi to a bDMARD, indicated that cycling to another JAKi may lead to longer treatment persistence (8). Our analysis using the OPAL dataset also includes a large number of patients treated using JAKi and shows that JAKi cycling is occurring frequently and across all lines of therapy. Our study with analyses separated by line of therapy is a valuable contribution supporting and extending the JAK-pot analyses. Further real-world data will continue to inform the selection of the best next therapy following JAKi discontinuation.

Our finding that treatment persistence was broadly similar across the different JAKi within each line of therapy is consistent with an analysis from Japan showing similar treatment discontinuation rates for TOF, BARI and the non-TNFi bDMARD sarilumab (19). Other studies have reported similar, or slightly longer, treatment persistence for JAKi compared to TNFi or other bDMARDs (9, 10). One Canadian study has reported slightly reduced persistence for TOF compared to bDMARDs (11). Although our study was not designed to compare persistence of JAKi against other drug classes, the estimated median persistence from our analysis is numerically consistent with these other studies.

As a retrospective analysis of observational data, there are important limitations that affect the interpretation of this study. Firstly, the differing durations of availability of the three JAKi drugs means that follow-up was restricted for UPA in particular and also BARI, which meant there was less time in which a treatment discontinuation event could occur for these drugs. We made a limited attempt to address these differing durations of follow-up by analysing the subgroup of patients who switched b/tsDMARD after 2020 (Suppl. Table S2). Secondly, patients were not randomly assigned to treatment groups and this real-world study was designed to be descriptive. For this reason, and the differing durations of availability, no comparisons are made between the three JAKi. Thirdly, there are missing data in this dataset, most notably a high percentage of disease activity measures were missing at baseline, and some missing disease activity measures were imputed using disease activity recorded at timepoints close to baseline. It is also possible that comorbidities are under-recorded. While we sought to exploit prescription date-stamps in the EMR software to complete missing medication start and stop dates, we acknowledge that these inferred dates may differ from the true missing dates.

A limitation of this study's design was that it was not set up to address safety. There was limited follow-up for these patients and the reasons for discontinuing JAKi treatment reported in the OPAL dataset are not independently adjudicated. In addition, one of the reasons for discontinuation as listed in the EMR is 'Completed treatment/no longer required'. We have reasons to believe that in this context this option does not mean the patient is in drug-free remission. Additional reasons, including drug free remission; have since been included in the software to provide better clarity for future studies. A very small percentage of patients (<10%) initiated a JAKi as a 1st line treatment with a DASCRP score corresponding with remission. This is most likely capturing patients who had received prior biologic or targeted synthetic treatment prior to transferring care to a rheumatologist participating in OPAL. Relatively higher risks of major cardiovascular events (MACE), VTE and malignancy have been observed for TOF *versus* TNFi in the randomised ORAL Surveillance trial. (20). Additional studies will facilitate a better understanding of these risks for all JAKi (21, 22).

In conclusion, we have shown high levels of TOF, BARI and UPA use across different lines of therapy for RA in Australia, with median treatment persistence for JAKi being high and longest when JAKi was used as first-line. While switches from JAKi to a TNFi were typically the most common after switching from JAKi in earlier lines of therapy, switching from one JAKi to another JAKi was also frequent. Patients who switched from JAKi to JAKi appeared to have higher rates of monotherapy at follow-up.

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