receiver operator characteristic curve. C-index values and 95% confidence intervals were calculated by fitting a univariate logistic regression model for: demographic and BL characteristics, Wk 12 disease activity measures, and change from BL at Wk 12 in disease activity measures. A multivariate logistic regression with stepwise model selection was also performed. The proportion of patients achieving Wk 24/26 CDAI REM/LDA was stratified by $\geq 50\%$ improvement from BL in swollen and/or tender joint count in 66/68 joints (SJC66/TJC68).

Results: A total of 1377 patients were included in the analysis. Across the 4 studies, CDAI REM and LDA were achieved in 11.0–28.4% and 50.0–58.6% of patients, respectively (Table 1). BL demographics and disease characteristics were weakly predictive (C-index <0.70) of Wk 24/26 CDAI REM (C-index 0.49–0.69) or LDA (C-index 0.47–0.65), with the exception of BL Health Assessment Questionnaire-Disability Index in SELECT-BEYOND, which was moderately predictive of CDAI REM (C-index 0.73). Changes from BL in disease activity measures at Wk 12 were weakly or moderately predictive of Wk 24/26 CDAI REM (Figure 1) or LDA. CDAI value at Wk 12 was strongly predictive (C-index >0.80) of Wk 24/26 CDAI REM or LDA. Disease Activity Score in 28 joints using CRP and pain at Wk 12 were strongly predictive of Wk 24/26 CDAI REM (except in SELECT-CHOICE). Physician's global assessment at Wk 12 was the only common predictor in the multivariate regression models for CDAI REM/LDA at Wk 24/26 across the 4 studies. A greater proportion of patients achieving $\geq 50\%$ improvement in SJC66 and TJC68 at Wk 12 achieved CDAI REM (16.5–37.8% vs 0–9.4%) or LDA (66.0–72.8% vs 20.9–35.7%) at Wk 24/26 than those who did not.

Conclusion: BL characteristics did not strongly predict response to UPA, but composite disease activity scores at Wk 12 predicted Wk 24/26 REM/LDA with UPA 15mg QD across MTX-naïve, MTX-IR, and TNFi-IR patients. $\geq 50\%$ improvement in SJC/TJC at Wk 12 was also associated with Wk 24/26 REM/LDA.

REFERENCES:

- [1] van Vollenhoven R, et al. *Arthritis Rheumatol* 2020;72:1607–20; 2. Genovese MC, et al. *Lancet* 2018;391:2513–24; 3. Fleischmann R, et al. *Arthritis Rheumatol* 2019;71:1788–800; 4. Rubbert-Roth A, et al. *N Engl J Med* 2020;383:1511–21.

Table 1. Achievement of CDAI LDA and REM at Wk 24/26^a

	SELECT-EARLY MTX-naïve UPA 15mg mono- therapy (n=317)	SELECT-COMPARE MTX-IR UPA 15mg + MTX (n=651)	SELECT-BEYOND TNFi-IR UPA 15mg + csDMARD (n=146)	SELECT-CHOICE TNFi-IR UPA 15mg + csDMARD (n=263)
Efficacy at Wk 24/26^a, n (%)				
CDAI REM (≤ 2.8)	90 (28.4)	150 (23.0)	16 (11.0)	60 (22.8)
CDAI LDA (≤ 10)	178 (56.2)	343 (52.7)	73 (50.0)	154 (58.6)

^a Wk 26 for SELECT-COMPARE only

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Figure 1b: 12 predictors for CDAI remission at Wk 24/26^a

^a Determined by a univariate logistic regression model. C-statistics provide a C-index value from 0.5 (chance predictor) to 1 (perfect predictor). Error bars indicate 95% CI. ^b Wk 26 for SELECT-COMPARE only.
CRP, C-reactive protein; DAS28(CRP), Disease Activity Score in 28 joints using C-reactive protein; HAQ-DL, Health Assessment Questionnaire Disability Index; PGA, Physician Global Assessment; PISA, Patient's Global Assessment; SJC36/68, swollen joint count in 36/68 joints; TJC28/68, tender joint count in 28/68 joints.

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POS0223

PATTERNS OF JANUS KINASE INHIBITOR CYCLING FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS IN REAL-WORLD CLINICAL PRACTICE: AN ANALYSIS OF THE OPAL DATASET

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Background: There are currently eleven biologic and targeted synthetic (b/ts) DMARDs acting via five different modes of action available for the treatment of RA in Australia. The cost of b/tsDMARDs is subsidized by government for patients that have active RA despite six months of combination csDMARD therapy. Once a patient is eligible, the clinician can prescribe the b/tsDMARD they deem to be the most clinically appropriate for the patient. In Oct 2015 the first JAK inhibitor (JAKi) became available in Australia (tofacitinib, TOF), baricitinib (BARI) became available in Sept 2018, and upadacitinib (UPA) in May 2020. Each of these oral tsDMARDs possess different selectivity profiles towards different members of the JAK family (JAK1–3 and Tyk2).

Objectives: The aim of this analysis was to determine the patterns of JAKi cycling in real-world practice in Australia.

Methods: Deidentified clinical data were sourced from the OPAL dataset, which is collected in a custom-built electronic medical record during the routine consultation¹. Data from patients >18 years with RA who commenced a b/tsDMARD between Jan-2007 and Dec-2020 were included in the analysis. A visual analytics software program was used to display data on medication initiation and cessation dates, and reasons for stopping tsDMARDs, which is recorded in the medical record at the time of the decision.

Results: At Dec 2020, 28% of the 52,190 patients with RA in the OPAL dataset were prescribed b/tsDMARDs. Of these patients, 3,850 (26.3%) were currently prescribed a JAKi with 51.4% receiving TOF, 29.2% BARI and 19.4% UPA. In 2020, JAKi initiations accounted for 48.8% of all initiations and 30.7% of 1st line initiations; an increase of 6.1% and 3.5% from 2019, respectively. The percentage of patients switching from a first line JAKi to a second line JAKi rather than an agent with another mode of action increased from 33.1% in 2019 to 42.6% in 2020. This is despite 26.2% in 2019 and 45.8% in 2020 of the patients switching to another JAKi citing lack of efficacy as the reason for JAKi discontinuation. In the period between May 2020, when a third JAKi (UPA) became available, and Dec 2020, the majority of patients switching from first line TOF or BARI to another JAKi switched to UPA (69.4% and 83.9%, respectively), whilst 30.6% of first line TOF patients switched to BARI (30.6%), and 16.1% of first line BARI patients switched to TOF in second line. The majority of patients switching from second line TOF or BARI to a third line JAKi switched to UPA (73% and 96%, respectively), with 27% of second line TOF patients switching to BARI and a very low number moving from second line BARI to TOF (4%). JAKi choice after a third line TOF or BARI was almost exclusively UPA (86.2% and 95.5%, respectively).

Conclusion: There has been significant and sustained uptake of JAKi for the management of RA in Australia and JAKi cycling is increasingly common in routine clinical care. Clinical outcomes and persistence following JAKi cycling requires further investigation.

REFERENCES:

- [1] Littlejohn GO, Tymms KE, Smith T, Griffiths HT. Using big data from real-world Australian rheumatology encounters to enhance clinical care and research. *Clin Exp Rheumatol*. Sep-Oct 2020;38(5):874-880.

Figure 1. Patterns of JAKi cycling for the management of rheumatoid arthritis in first, second and third line switching.

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POS0224

SELECTIVITY OF CLINICAL JAK INHIBITORS AND THE IMPACT ON NATURAL KILLER (NK) CELL FUNCTIONAL RESPONSES

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Background: Janus kinase (JAK) inhibitors (JAKinibs) show similar efficacy in rheumatoid arthritis (RA). However, in vitro studies have shown differences in JAK selectivity profiles for baricitinib (BARI), tofacitinib (TOFA), upadacitinib (UPA) and filgotinib (FIL).^{1,2} These lead to distinct pharmacologic profiles in cellular signaling assays that may impact clinical efficacy or safety¹. NK cells are innate lymphocytes important in anti-pathogen responses and immune surveillance, which function via production of cytokines and cell killing³. NK cell proliferation and IFN γ production are JAK-dependent pathways and may be modulated by JAKinibs. Clinical findings show transient decreases in NK cell numbers in patients treated with JAKinibs, but the link to safety is unclear⁴.

Objectives: To extend upon findings in proximal cell signaling assays, we compared the selectivity and potency of clinical JAKinibs on NK cell function by assessing proliferation mediated by IL-15 (JAK1/3) and IFN γ production driven by IL-12 (JAK2/TYK2)+IL-18.

Methods: NK cells were isolated from healthy donor PBMC, incubated in vitro with 8 concentrations of each evaluated JAKinib (TOFA, BARI, FIL, FIL metabolite, UPA) and stimulated with IL-15 for proliferation or IL-12/18 for IFN γ production. Proliferation was assessed by Cell Trace dye dilution after 6 days and IFN γ production by intracellular flow cytometry 4hrs post-stimulation. Half maximal inhibitory concentration (IC₅₀) values were calculated for CD56^{bright}, CD56^{dim}, and total NK cells. Steady-state pharmacologic profile over a clinical dosing interval was modeled using concentration-time profiles from JAKinib population pharmacokinetic data in RA subjects under the therapeutic dose⁵⁻⁷. For each JAKinib, the time above IC₅₀ and average daily inhibition of IFN γ or proliferation were calculated for each NK cell population in each donor.

Results: Cellular assays in purified NK cells showed dose-dependent inhibition of IL-15-induced proliferation by all JAKinibs with TOFA showing the highest average inhibition and time above IC₅₀ (35-60% inhibition for 8-15 hrs; TOFA>UPA>BARI>FIL). The differences between JAKinibs are in line with differences in pSTAT inhibition downstream of IL-15¹. Interestingly, IL-12/18-induced production of IFN γ , which is mediated via JAK2/TYK2 (IL-12) and non-JAK dependent pathways (IL-18), showed weaker inhibition for all compounds. Moreover, all JAKinibs showed <25% average inhibition of IFN γ production over 24hrs and did not show any time above IC₅₀ for IFN γ production or pSTAT4 inhibition at clinical doses. CD56^{dim} and CD56^{bright} sub-populations of NK cells are proposed to have distinct functions and unique expression of surface receptors. Analysis of the IC₅₀ for pSTAT4 and IFN γ production showed ~2-10-fold weaker inhibition by JAKinibs in CD56^{bright} NK cells, suggesting less dependence on JAK-dependent signals in CD56^{bright} NK cells than CD56^{dim} NK cells.

Conclusion: NK cell proliferation depends on JAK1 and JAK3-mediated signaling and is differentially inhibited at clinical doses of distinct JAKinibs. In contrast, functional responses downstream of JAK2/TYK2-dependent IL-12/18 were

not substantially inhibited by any of the JAKinibs studied. Inhibition of functional and proliferative responses in purified NK cells aligned well with proximal pSTAT inhibition. JAKinib modulation of NK cell proliferation, but not response to IL-12, reflects unique pharmacologic profiles of the drugs studied and could be one component underlying clinical safety observations, including increased risk of viral infections or malignancy⁴.

REFERENCES:

- [1] Traves PG et al. *Ann Rheum Dis* 2021 (in press)
- [2] McInnes IB, et al. *Arthritis Res Ther* 2019;21:183.
- [3] Cooper MA, Fehniger TA, Caligiuri MA. *Trends Immunol* 2001 Nov;22(11):633-40.
- [4] Winthrop KL. *Nat Rev Rheumatol* 2017; 13(4):234-243
- [5] Zhang X, et al. *CPT Pharmacometrics Syst Pharmacol* 2017;6(12):804-13.
- [6] CDER. Application Number: 203214Orig1s000. NDA 203214: Tofacitinib.
- [7] Klunder B et al. *Clin Pharmacokinet* 2019;58(8):1045-58.

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POS0225

RISK OF MAJOR CARDIOVASCULAR EVENT ACROSS JAK INHIBITOR TREATED PATIENTS: ANALYSIS OF A NATIONAL CLAIM DATABASE

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Background: Inhibiting a specific JAK may impede more than one pathway, explaining both the efficacy and adverse effects observed with JAK inhibitors (JAKi). Among those, there have been recent concerns about potential thromboembolic risks with these drugs. As patients enrolled are not representative of all patients who may receive JAKi, data from trials are unlikely to provide definitive answers. Real impact of JAKi in real life on major cardiovascular events is not known.

Objectives: To evaluate the risk of venous and arterial thromboembolic events with the use of JAKi in a real-world setting.

Methods: A self-controlled case series analysis (method in which individuals act as their own control) was performed using data from the French national health-care insurance system SNDS ("Système National des Données de Santé"), which included all anonymized individual level data about sociodemographic data, outpatient healthcare dispensed, hospital discharge summaries, and registration status for a list of 30 long term diseases. All patients treated by JAKi (baricitinib or tofacitinib) for rheumatoid arthritis, psoriasis arthritis and/or inflammatory bowel disease, and with at least one thromboembolic event (venous (VTE): deep vein thrombosis (DVT), pulmonary embolism (PE), arterial (ATE): acute coronary syndrome (ACS), myocardial infarction (MI), transient ischemic attack (TIA) and stroke) between 2017/11/01 and 2019/06/30 were included in the study. Associations were evaluated by incidence rate ratios (IRR), which compare the rate of events during exposed periods with rate of event during all other observed time periods. Exposed periods were defined as i) exposure to JAKi, ii) the month following exposure (post-exposure 1-30 days), and iii) long-term post-exposure (31 to 60 days). A pre-exposure period of 7 days was individualized to identify event-dependent probabilities of exposure and potential reverse causality bias, and all other periods were considered as non-exposed periods.

Results: Among the 5,870 patients treated with JAKi between 2017/11/01 and 2019/06/30, 94 presented an incident thromboembolic event and were included. Almost two thirds were female (n=61, 64.9%), and median age was 65.4 [IQR: 55.5; 75.8] years. Most of patients have a rheumatoid arthritis (n=91, 96.8%), 62 (66.0%) were treated by baricitinib, and 32 (34.0%) by tofacitinib. Almost half (n=42, 44.7%) presented a venous thromboembolism, mainly DVT (n=31, 33.0%), and 52 (55.3%) presented an arterial thromboembolism, mainly MI (n=16, 17.0%) and stroke (n=14, 14.9%). Eleven patients (11.7%) died during the study period. The median time of occurrence of VTE was 4.3 [IQR: 2.5; 8.9] months, and 6.1 [IQR: 3.3; 9.2] months for ATE.