Figure 1. Modification of Treg (A) and Th17 (B) populations at baseline and after one month of Tofacitinib treatment in RA patients.

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AB0356

TARGETING THE RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLAST VIA CYCLIN DEPENDENT KINASE INHIBITION (TRAFIC): A PHASE 1B STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE OF SELICICLIB FOR REPURPOSING IN RHEUMATOID ARTHRITIS

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Background: Current rheumatoid arthritis (RA) therapeutics target immune inflammation and are subject to ceiling effects, with non-response observed in a third of recipients together with low remission rates. Synovial fibroblasts (SFs) are stromal cells not yet targeted in RA, whose hyperplastic and proliferative properties drive inflammation and tissue destruction. Seliciclib (R-roscovitine) is an orally available cyclin-dependent kinase (CDK) inhibitor that suppresses SF proliferation and ameliorates inflammatory arthritis in rodents.

Objectives: To determine the maximum tolerated dose (MTD) of seliciclib in patients with active RA despite anti-TNF, with or without background conventional disease modifying anti-rheumatic drugs (cDMARDs). Safety and pharmacokinetics (PK) were also evaluated.

Methods: A restricted, one-stage Bayesian continual reassessment method (CRM) determined MTD based on a target dose-limiting toxicity (DLT) probability of 35%. RA patients (DAS28 ≥ 3.2) were recruited sequentially to cohorts of 3 subjects each. Cohort 1 received 400mg seliciclib daily for 4 consecutive days each week for 4 weeks, added to existing therapy. Each subsequent cohort received a dose determined by the toxicity-based CRM algorithm, calculated upon conclusion of the previous cohort. Safety was assessed through adverse event (AE) monitoring. Associations with relevant PK parameters were sought.

Results: 15 anti-TNF recipients were enrolled, 10 of whom were also taking cDMARDs (median DAS28 4.9). Application of the CRM algorithm prompted one dose increment during the study (to 600mg for cohort 2), but reversion to 400mg for subsequent cohorts (Figure 1A). After treatment of 5 cohorts, 400mg was determined the MTD, with a DLT probability of 0.35 (CI 0.18-0.52; Figure 1B). 6 patients experienced DLTs, of which two were classified as serious AEs (SAEs) in keeping with the safety profile of seliciclib; these are summarised in Table 1. Of 43/65 total AEs reported at any dose that did not contribute to a DLT, 26 were possibly, probably or definitely related to seliciclib; 19 of these 26 were mild, 7

moderate and none severe. The most frequent AE was mild nausea. No relationship of safety and/or tolerability with concomitant cDMARD use or PK was seen.

Table 1. ^AOutcome of contributory AEs/SAE at close of follow-up. ^BSAEs classified as 'expected'. DLT: dose limiting toxicity; N+V: nausea, vomiting.

DLT	Seliciclib dose (mg)	Doses received	Contributing AEs	Contributing SAEs	Description	Outcome ^A
1	400	8	3	0	Constipation, N+V, liver injury; fatigue.	Resolved
2	600	4	3	0	Constipation, N+V.	Resolved
3	600	1	0	1 ^B	Fever, N+V, renal injury.	Resolved
4	400	8	3	1 ^B	Constipation, N+V, jaundice, liver injury.	Resolved
5	400	8	4	0	Fever, dizziness, liver injury.	Resolved
6	400	8	9	0	Dizziness, N+V, liver injury, bilirubin rise.	Persistent AST rise

Conclusion: The MTD of seliciclib has been defined for RA. No unexpected safety concerns were identified to preclude ongoing evaluation in patients, which focuses on clinical, radiological and biological indicators of efficacy.

Figure 1. A. Dose limiting toxicity (DLT) occurrence by cohort and dose level (DLTs shown in red). B. Bayesian posterior probability of DLT at each dose level (with 90% confidence interval) following completion of cohort 5. Red point indicates value closest to target of 0.35, and hence maximum tolerated dose (MTD).

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AB0357

USE OF TOFACITINIB AND REASONS FOR DISCONTINUATION IN CLINICAL PRACTICE

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Background: Tofacitinib is an oral JAK 1 and 3 inhibitor for the treatment of moderate to severe active rheumatoid arthritis (RA) or psoriatic arthritis (PsA) in adults with inadequate response or intolerant to one or more conventional disease-modifying antirheumatic drugs (cDMARDs). Since its approval by the European Medicines Agency (EMA), there is limited data about its use in daily practice in Europe.

Objectives: To describe rates and reasons for discontinuation of Tofacitinib in patients with RA and other inflammatory conditions

Methods: We identified patients with a prescription for tofacitinib at our academic center from January 2017 to January 2020. Patients were treated according to their rheumatologist evaluation following standards of care. The following variables were retrospectively collected from the electronic

medical chart: age, gender, diagnosis, date of treatment initiation, date and reasons for treatment discontinuation, the use of concomitant or previous cDMARDs and of biologics. A comparison between patients continuing and stopping tofacitinib was performed through χ^2 or t-test for qualitative and quantitative variables, respectively. Survival analysis was done by Kaplan-Meier method

Results: Ninety patients receiving tofacitinib were identified, 81 with RA, 6 with PsA, 1 with Dermatomyositis, 1 with Sjögren's and 1 with juvenile idiopathic arthritis. Table 1 shows the baseline characteristics. 84% percent patients were women and the mean (SD) age was 58.5 (14.2) years. 51% patients started tofacitinib in monotherapy. When used, methotrexate was the most frequent cDMARD (61.3%); 10% patients used tofacitinib as first line after cDMARD and the majority used it after 1 or 2 previous biologics (46.7%).

Table 1. Baseline characteristics of the patients

	All patients (n=90, 100%)	Continue Tofacitinib (n=58; 64%)	Not continue Tofacitinib (n=32; 35.5%)	p-value
Female (%)	76 (84.4)	48 (82.7)	28 (87.5)	0.55
Age (year) – mean (SD)	58.5 (14.2)	58 (12.9)	59.5 (16.5)	0.63
Diagnosis				0.66
Rheumatoid arthritis	81 (90)	52 (89.6)	29 (90.6)	
Psoriatic arthritis	6 (6.7)	4 (6.8)	2 (6.2)	
Other	3 (3.3)	2 (3.4)	1 (3.1)	
Treatment duration (months) – mean (SD)	10.6 (6.9)	11.9 (7.3)	8.2 (5.5)	0.02
Prednisone (mg) – mean (SD)	1.75 (3.2)	1.20 (2.5)	2.73 (4.1)	0.03
Monotherapy (%)	46 (51.1)	28 (48.2)	18 (56.2)	0.244
Concomitant csDMARDs (%)	44 (48.8)	30 (51.7)	14 (43.7)	0.62
Methotrexate (%)	27 (30)	17 (29.3)	10 (31.2)	
Leflunomide (%)	10 (11.1)	8 (13.7)	2 (6.2)	
Other (%)	7 (7.7)	5 (8.6)	2 (6.2)	
Prior biologic treatment				0.13
None (%)	9 (10)	6 (10.3)	3 (9.3)	
1-2 (%)	42 (46.6)	28 (48.2)	14 (43.7)	
≥3 (%)	39 (43.3)	24 (41.3)	15 (46.8)	

Survival rates when used as first or second line were 85% at 6 months and 70% at 12 months; when used as third line or further, 76% and 70%, respectively (graphic 1). Factors associated to tofacitinib discontinuation were treatment duration and baseline prednisone dose. In contrast concomitant csDMARD and number of previous biologics were not. Reasons for tofacitinib discontinuation were: lack/loss of efficacy 46.9%, adverse events 50% (including intolerance -22%- herpes zoster -16%-, other infections 12%) and others.

Conclusion: Tofacitinib in our experience is mostly used in RA patients after biologic failure. Overall survival rate at 12 months was good regardless line of therapy. Adverse event rates were similar to other biologic treatments. Herpes zoster was the most common infectious AE.

Graphic 1:

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AB0358 REDUCTION OF WHITE BLOOD CELL COUNT PREDICTS THE EFFICACY OF BARICITINIB, DOES NOT OF TOFACITINIB FOR RHEUMATOID ARTHRITIS.

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Background: Pairing Janus kinase (JAK) 1/JAK3 signaling mediates lymphocyte proliferation and differentiation while pairing JAK2/JAK2 signaling is essential in myelopoiesis, erythropoiesis, and platelet production by facilitating signaling mediated by granulocyte-macrophage colony stimulating factor and erythropoietin. Tofacitinib (TOF) preferentially inhibits JAK1 and JAK3, while baricitinib (BAR) inhibits JAK1 and JAK2 *in vitro* (1). However, the difference in the efficacy and the clinical courses between TOF and BAR in patients with rheumatoid arthritis (RA) remains unclear.

Objectives: The objective of this study was to compare TOF and BAR in efficacy and changes in peripheral blood cell counts. We hypothesized that the efficiency of BAR was related to the decline in the blood cell counts, but that of TOF was not in patients with RA.

Methods: We conducted a multicenter, 24 week-retrospective observational study. All RA patients received TOF (n = 43) or BAR (n = 26) treatment at Tama-Hokubu Medical Center and Tama Medical Center from December 2013 to March 2019 were included.

Results: Baseline characteristics were similar between both groups; age 59.1 and 65.0 years old, disease duration 164.1 and 111.7 months, C-reactive protein 1.98 and 2.22 mg/ml, rheumatoid factor positive 76.7 % and 84.0 %, anti-citrullinated peptide antibody positive 78.9 % and 78.8 %, methotrexate combination 81.4 % and 69.2 %, the number of previous treatment of biologic or targeted disease-modifying antirheumatic drugs were 2.7 and 2.8, for TOF and BAR, respectively (mean).

Simplified Disease Activity Index (SDAI) at baseline were similar between the groups (TOF 20.77, BAR 19.15). There was no significant difference in efficacy between the both groups at week 24 (SDAI remission: TOF 3 (7%), BAR 6 (23.1%), p = 0.054, SDAI low disease activity (LDA): TOF 21 (48.8%), BAR 17 (65.4%), p = 0.181).

Among those who achieved SDAI LDA at week 24 in the BAR group, significant decrement of white blood cell (WBC) counts at week 12 and 24 and of neutrophil counts at week 4, 12 and 24 were observed (p < 0.05, Table). These decrements of cell count were not observed in patients who did not achieve LDA or in patients in the TOF group. Platelets and hemoglobin (data not shown) had no significant change in all groups.

Conclusion: Clinical efficacy of TOF and BAR in RA was comparable in our cohort. A significant decrease of WBCs and neutrophils was associated with LDA achievement at week 24 in the BAR group. This could be explained by the inhibition of myelopoiesis through JAK2 signaling.

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