levels, while gene expression of *STAT3*, *STAT4*, *STAT5A*, *JAK1*, *JAK3* and all studied SOCSs was significantly suppressed. Baseline STAT phosphorylation levels in T cells and monocytes and *SOCS3* expression in PBMCs correlated with treatment response.

Conclusion: Tofacitinib suppresses multiple JAK-STAT pathways in RA patients *in vivo*. Baseline JAK-STAT signaling profile may be applicable as a prognostic marker for treatment response to tofacitinib.

REFERENCES:

- [1] McInnes, I. B., Buckley, C. D. & Isaacs, J. D. Cytokines in rheumatoid arthritis-shaping the immunological landscape. *Nature Reviews Rheumatology* vol. 12 63–68 (2016).
- [2] Schwartz, D. M., Bonelli, M., Gadina, M. & O'Shea, J. J. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat. Rev. Rheumatol.* 12, 25–36 (2016).

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AB0251

INCREASED ACCUMULATION OF ERYTHROCYTE METHOTREXATE POLYGLUTAMATES DURING EARLY PHASE SUBCUTANEOUS VERSUS ORAL METHOTREXATE TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS

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Background: Optimal dosing of methotrexate (MTX) for individual rheumatoid arthritis (RA) patients to achieve adequate disease control is an ongoing challenge. Assessment of erythrocyte MTX-polyglutamates (PGs) levels has been employed as a tool to monitor clinical response of RA patients in the first 3-12 months of treatment and MTX-PG₂₋₄ and total MTX-PGs were associated with a lower DAS28 over 9 months.¹ However, data from earlier time points, MTX-PG₆ and per route of administration are unavailable.

Objectives: To investigate the pharmacokinetics and -dynamics of erythrocyte MTX-PG accumulation in RA patients receiving oral or subcutaneous MTX in the early phase (1, 2, and 3 months) of MTX treatment initiation.

Methods: In a clinical prospective cohort study (MeMo study (NTR7149)), newly diagnosed RA patients were administered oral (n=24) or subcutaneous (n=22) MTX, mostly according to the COBRA-light schedule (start 10mg MTX, increased to 25mg MTX in 8 weeks). At 1, 2, and 3 months after start of therapy, blood was collected and individual MTX-PGs (MTX-PG₁ – MTX-PG₆) were analyzed in erythrocytes at a minimal detection limit of 1 nmol/L, using a validated UHPLC-MS/MS method with labeled internal standards.¹ Dosing, concomitant treatments and DAS28-ESR assessments were in conformity with clinical practice. Adverse events were recorded.

Results: 46 consecutive patients were included in this study; 76% female, mean age: 57.8 years, BMI: 25.8, 20% smokers, mean baseline DAS28-ESR: 3.5. Notwithstanding marked interpatient variability, patients starting subcutaneous MTX had accumulated significantly higher (approximately 2-fold) long chain MTX-PGs (MTX-PG₄₋₆) when compared to patients in the oral MTX group at 1 and 2 months (Figure 1A, Table 1). Similarly, MTX-PG₁₋₆ and MTX-PG₃ accumulation were higher in subcutaneous MTX-users at month 1 (p=0.022 and p=0.011) compared to the oral group (median 68.6 nmol/L (IQR:40.5) vs 51.9 (55.6) and 17.4 (11.1) vs 11.2 (15.6), respectively (Figure 1B, Table 1).

Table 1. Linear regression of MTX-PG levels and administration route, corrected for age, baseline DAS28, smoking, BMI, eGFR and MTX dose.

month	B (P-value) 1	B (P-value) 2	B (P-value) 3
MTX-PG ₁₋₆	1.65 (0.022)	1.51 (0.073)	1.30 (0.233)
MTX-PG _{1,2}	1.13 (0.599)	1.19 (0.470)	1.12 (0.623)
MTX-PG ₃	1.75 (0.011)	1.51 (0.071)	1.19 (0.439)
MTX-PG ₄₋₆	1.97 (0.036)	2.04 (0.033)	1.55 (0.136)

Mean MTX dose at baseline was 10.5mg (SD 1.5) for both groups, 15.4 (4.4) and 16.8 (1.8) at 1 month and 22.8 (3.9) and 22.4 (5.2) at 2 months for oral and subcutaneous use respectively.

DAS28 decreased with 1.6 in the oral group and 1.1 in the subcutaneous group (p=0.382). With and without corrections for age, baseline DAS28, eGFR, MTX dose (1 month before sampling), smoking and BMI, no significant relation between MTX-PG concentrations and DAS28 was observed during the first 3 months of treatment.

43 patients reported any side effect, mostly headache and dizziness, which was similar in both groups and uncorrelated with MTX-PG levels.

No association was found between MTX-PG₁ levels and number of days between timing of blood withdrawal and last administration.

Figure 1. Erythrocyte long chain MTX-PG (A) and total MTX-PG (B) accumulation in RA patients of the first 3 months of oral (C) or subcutaneous (D) MTX administration. At 3 months, 18 patients using oral and 18 patients using subcutaneous MTX were still continuing MTX treatment. Medians and IQR are depicted.

Conclusion: This study shows the feasibility of measuring erythrocyte MTX-PGs early on in the treatment of RA patients with MTX and demonstrated significantly higher accumulation of MTX-PGs following subcutaneous versus oral MTX administration. Early phase erythrocyte MTX-PG analyses may hold potential for positioning in optimizing individual patient MTX dose scheduling.

REFERENCES:

- [1] de Rotte MC, et al. Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in patients with rheumatoid arthritis. *Ann Rheum Dis* 2015(74):408-14.

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AB0252

EFFICACY OF A SECOND JANUS KINASE INHIBITOR THAT WAS SWITCHED FOR DIFFICULT-TO-TREAT RA IN CLINICAL PRACTICE

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Background: In clinical practice, when refractory rheumatoid arthritis (RA) is present, of which the definition implies previous use of at least two biologic disease-modifying antirheumatic drugs (bDMARDs) (generally tumour necrosis factor inhibitors (TNFis)), the next treatment choice often made is a bDMARD of another class (non-TNFis) [1]. However, patients who are inadequately responding to bDMARDs need new treatment options because subsequent bDMARDs treatment reduces their response [2]. Janus Kinase inhibitors (JAKis) are the first targeted synthetic DMARDs (tsDMARD) licensed for the treatment of RA with comparable efficacy to bDMARDs. Unlike the single cytokine targeting approach of bDMARDs, JAKis are specifically designed to inhibit intracellular signalling molecules common to the receptors of multiple inflammatory cytokines implicated in RA pathogenesis. The choice of therapeutic agents for refractory RA is increasing, and its efficacy is expected. On the other hand, it is also true that some patients discontinued JAKis at a rate that cannot be overlooked because

of insufficient efficacy. Difficult-to-treat (D2T) RA is defined as refractory to two or more b/ts DMARDs with different mechanisms of action, with active and progressive disease, as published by Eular(3)

Objectives: To evaluate real world efficacy of approved JAKis switching in patients with D2T RA who were unable to control their disease activity due to insufficient efficacy despite the sequential use of multiple bDMARDs and JAKis, focusing on the drug retention rate.

Methods: In our hospital, RA was diagnosed according to the 1987 or 2010 classification criteria, and when two or more bDMARDs (including both TNFis and non-TNFis) were inadequately effective, it was defined as D2T RA. We retrospectively investigated patients who switched to JAKis for D2T RA. The drug retention rate was investigated by the Kaplan-Meier method, and the difference was tested by the Logrank test.

Results: The 1-year retention rate of JAKis for D2T RA was 50.8% in TOF 38 cases [28 women, age average 70.2 years, disease duration average 12.4 years, past bDMARDs use average 3.5 drugs, MTX combination 9 cases, DAS28 ESR average 4.11] and 66.3% in BAR 35 cases [26 cases, 73.0 years old, 14.8 years, 4.17 agents, 9 cases, 3.68], and there was no significant difference ($P = 0.30$). Among them, there were 17 cases [11 cases, 70.6 years old, 13.5 years, 4.18 drugs, 2 cases, 3.65] of switching between JAKis, all of which were switching from TOF to BAR. The 1-year retention rate was 45.8% [reason for discontinuation: insufficient effect in 3 cases, adverse events in 6 cases], which was not significantly different but tended to be lower than 72.7% [reason for discontinuation: insufficient effect in 1 case, adverse event in 2 cases, patient's convenience in 1 case] in 16 patients [13 cases, 76.3 years old, 17.1 years, 3.19 drugs, 7 cases, 3.69] who received BAR as the first JAKi for D2T RA patients ($P = 0.089$).

Conclusion: Although the number of cases is small in the retrospective survey, it is suggested that the retention rate of BAR switched to D2T RA may be slightly lower in patients with a history of TOF discontinuation due to insufficient efficacy than in JAKi naive patients. It is expected that the number of new JAKi usage cases will increase in the future, and it is necessary to consider switching between other JAKis in addition to switching from BAR to TOF.

REFERENCES:

- [1] Smolen JS, Landewe R, Bijlsma J et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960-77.
- [2] Rendas-Baum R, Wallenstein GV, Koncz T et al. Evaluating the efficacy of sequential biologic therapies for rheumatoid arthritis patients with an inadequate response to tumor necrosis factor- α inhibitors. *Arthritis Res Ther* 2011;13:R25.
- [3] Nagy G, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31-35. doi:10.1136/annrheumdis-2020-217344.

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AB0253

COMPARISON OF PHARMACODYNAMICS OF METHOTREXATE AS METHOTREXATE-POLYGLUTAMATES CONCENTRATIONS IN RHEUMATOID ARTHRITIS; INTERIM DATA EVALUATION OF MIRACLE STUDY CONDUCTED IN JAPAN, KOREA AND TAIWAN

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Background: Methotrexate (MTX) is the first-line therapy for rheumatoid arthritis (RA). The concentrations of MTX-polyglutamates (PG) in erythrocytes, an active form of MTX, are useful markers for the optimal usage of MTX in patients with RA. The concentrations of MTX-PG have been reported to be different between Japanese and Caucasians. However, the difference among Asian ethnicity remains unclear.

Objectives: To examine MTX-PG concentrations in association with MTX dose during the first 24 weeks after the initiation of MTX for newly diagnosed RA patients in Japan, Korea and Taiwan.

Methods: MIRACLE study is a multicenter, open-label, randomized, 48 weeks interventional study conducted in Japan, Korea and Taiwan to evaluate non-inferiority of low dose to high dose of MTX as an add-on therapy to adalimumab in 300 patients with RA who do not achieve remission after 24 weeks MTX monotherapy in stipulated dosage. In the first 24 weeks, MTX was started at 6 to 8 mg/week for newly diagnosed RA patients, and promptly escalated to the maximum tolerable dose in 12 weeks in principle. This interim data evaluation was intended to investigate the differences among countries in the relationship between MTX dose, safety and MTX-PG concentrations in erythrocytes during the first 24 weeks. The efficacy of the treatment is not included at this point.

Results: A total of 166 patients (106 in Japan, 35 in Korea, 25 in Taiwan) were included in this interim data. The age at treatment initiation was 57.2 years old on average and female was 79.5%. The time course changes in total and individual MTX-PG levels differed in the three countries. At 24 weeks, whereas the mean total MTX-PG concentrations were comparable (112.9 nmol/L in Japan, 104.4 nmol/L in Korea, and 115.7 nmol/L in Taiwan) with a dose of MTX of 12.3mg/week, 14.1mg/week, and 12.2mg/week, respectively, the individual MTX-PG concentrations were different. The MTX-PG1 and MTX-PG2 concentrations were lower in Korea than Japan and Taiwan whereas MTX-PG3, MTX-PG4 and MTX-PG5 concentrations were the highest in Korea.

Conclusion: The distribution of short-chain and long-chain MTX-PG concentrations were various among Asian countries despite similar dose of MTX administration: NCT03505008.

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