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:**


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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 with MTX-PG1-2 and total MTX-PGs were associated with a challenge. Assessment of erythrocyte MTX-polyglutamates (PGs) levels has been 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 use of MTX-PGs 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 10 mg MTX, increased to 25 mg 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: 3.1. Notwithstanding marked interpatient variability, patients starting subcutaneous MTX had accumulated significantly higher (approximately 2-fold) long chain MTX-PGs (MTX-PG1-2) when compared to patients in the oral MTX group at 1 and 2 months (Figure 1A, Table 1). Similarly, MTX-PG1–6 and MTX-PG 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 mmol/L (IQR;69.5–95.4) versus 51.9 (55.6) and 17.4 (11.1) to 11.2 (15.8), respectively (Figure 1B, Table 1).

**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:**


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**Disclosure of Interests:** Renske Hebing Grant/research support from: Pfizer, Ittai Muller: None declared, Marry Lin: None declared, Sohaila Mahmoud: None declared, Sandra Heil: None declared, Willem Lems: None declared, Michael Nurmohamed: None declared, Robert De Jonge: None declared, Gerrit Jansen: None declared

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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 includes 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

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 1.5 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-PG, levels and number of days between timing of blood withdrawal and last administration.

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

<table>
<thead>
<tr>
<th>Month</th>
<th>p (P-value)</th>
<th>p (P-value)</th>
<th>p (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.05 (0.002)</td>
<td>1.51 (0.007)</td>
<td>1.06 (0.253)</td>
</tr>
<tr>
<td>2</td>
<td>1.13 (0.599)</td>
<td>1.19 (0.470)</td>
<td>1.12 (0.623)</td>
</tr>
<tr>
<td>3</td>
<td>1.75 (0.011)</td>
<td>1.51 (0.071)</td>
<td>1.19 (0.439)</td>
</tr>
<tr>
<td>4</td>
<td>1.97 (0.036)</td>
<td>2.04 (0.033)</td>
<td>1.55 (0.136)</td>
</tr>
</tbody>
</table>