Determinants of erythrocyte methotrexate polyglutamate concentrations in patients treated with methotrexate

Authors: Sundaresan J.[1], Hamelink W. J .[1], Hebing R.C.F[2,3], van de Meeberg M.M.[4,5], Janssen Bonás M.[6], de Jonge R.[1], de Rotte M. C. F. J.[1], Bulatović-Ćalasan M.[1,7]

1 Laboratory Specialized Diagnostics & Research, Department of Laboratory Medicine, Amsterdam UMC, Amsterdam, the Netherlands

2 Amsterdam Rheumatology and Immunology Center, Amsterdam UMC and Reade, Amsterdam, The Netherlands

3 Department of Clinical Pharmacy, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

4 Department of Gastroenterology and Hepatology, Amsterdam UMC, AGEM Research Institute, Amsterdam, The Netherlands

5 Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands

6 ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands

7 Department of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

Background

Erythrocyte methotrexate polyglutamate ($MTXPG_{1-5}$) concentrations correlate with therapy efficacy in various immune mediated inflammatory diseases (IMID) including Rheumatoid arthritis (RA), Juvenile idiopathic arthritis (JIA), Crohn's disease (CD) and sarcoidosis. We aimed to identify clinical and biochemical determinants of the accumulation of MTXPGn in erythrocytes across these IMIDs treated with methotrexate (MTX).

Methods

Erythrocyte-MTXPGn concentration data (quantified after 3 months of MTX treatment) from 543 patients diagnosed with RA, JIA, CD, and sarcoidosis, treated with MTX between 2006 and 2020 were considered in this study. All MTX dose were standardized to body surface area (BSA) based MTX dose for between disease comparison. All analysis were performed in R (v4.2.1). Age, gender, BMI, smoking, BSA MTX-dose, route of administration (oral as reference), eGFR, DMARD, prednisone and folic acid use were all analyzed as possible determinants using multivariate linear regression modelling.

Results

The median (interquartile range) of body surface area (BSA) based MTX dose was 10.3 mg/m^2/week (7.9-13.0). The median (interquartile range) of sum of $MTXPG_{3-5}$ was 60.2 nmol/L packed erythrocytes (32.6-92.0). The $MTXPG_{1-5}$ concentrations across diseases were similar between the diseases. Accumulation of sum of $MTXPG_{3-5}$ (long-chain MTXPGs) was associated with age (β 1.0; p=0.003), BMI (β -0.98; p=0.01), subcutaneous administration (β 1.45; p=0.001), MTX dose (β 1.03; p=0.004), prednisone use (β-0.69; p=0.007), use of other anti-rheumatic drugs (DMARD) (β -0.82; p=0.008) and kidney function (β -0.99; p=0.04).

Conclusion

This is the first study to estimate factors that determine the accumulation of $MTXPG_n$ in erythrocytes in a large cohort of various IMID patients. Similar to previous studies, higher age, MTX-dose and subcutaneous administration had a positive association, while kidney function and BMI had a negative association with MTX-PG accumulation. DMARD use was newly identified as having a negative association with long-chain $MTXPG_n$ accumulation. Understanding the factors that affect $MTXPG_n$ in erythrocytes can facilitate therapeutic drug monitoring (TDM) of MTX and contribute to development of personalized treatment.

Keywords: Methotrexate, erythrocyte methotrexate-polyglutamates, immune-mediated inflammatory diseases